LYMPHOGRANULOMATOSIS BENIGNA

A CLINICAL AND HISTO-PATHOLOGICAL STUDY OF ITS RELATION TO TUBERCULOSIS

BY

LENNART ZETTERGREN

ALMQVIST & WIKSELLS BOKTRYCKERI AB
UPPSALA 1954

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AKADEMISK AVHANDLING

som med tillstånd av Medicinska Fakulteten
vid Uppsala Universitet för vinnande av medicine
doktorsgrad framlägges till offentlig granskning
å Patologiska Institutionens hörsal
måndagen den 24 maj 1954
kl. 10 f. m.

av

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Med. lic., Vg.

UPPSALA 1954
ALMQVIST & WIKSELLS BOKTRYCKERI AB

FROM THE INSTITUTE OF PATHOLOGY, UNIVERSITY OF UPPSALA, SWEDEN
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Also published as Supplement 5 to

ACTA SOCIETATIS MEDICORUM
UPSALIENSIS

TRANSLATED BY DR ANN SYNGE

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LEIDEN

Almqvist & Wiksells
BOKTRYCKERI AKTIEBOLAG
UPPSALA 1954

Contents

Introduction 5

Chapter 1. History 7

Chapter 2. Clinical observations 14
Pulmonary symptoms 17
Lymphadenopathy 20
Splenic involvement 21
Hepatic involvement 21
Skin lesions 22
Febris uveoparotidea subchronica (Heerfordt) 23
Bone lesions 24
Lesions of the central nervous system 25
The tuberculin reaction 26

Chapter 3. Lymphogranulomatosis benigna and the bilateral hilar lymphoma syndrome 28

Chapter 4. Histopathology 33
The epithelioid cells 34
The giant cells 36
The inclusion bodies 38
The asteroid body 38
The Schaumann body 41
Regressive changes 47
Caseous necrosis 47
Fibrinoid necrosis 47
Perifocal inflammatory reaction 49
The reticulum. Indurative changes 50
The blood vessels 51
Microscopical differential diagnosis 52

Chapter 5. Etiology 54
The virus theory 54
The mycotic theory 55
The allergic theory 55
The tuberculous theory 56

Own Investigations

Chapter 6. The problems. Aim of the investigation 64

Chapter 7. Material and methods 66
Nature of the material 66
Primary microscopical diagnosis 66
Microscopical analysis 67
Clinical analysis 67
Division of the material 67

Chapter 8. Series I. Lymph nodes with bacilli present. Tuberculosis chronica hyperplastica . . . 68
Age and sex distribution . . . 68
Clinical picture of the lymphadenitis . . . 68
Clinical relationship to classical tuberculosis . . . 69
Clinical relationship to l.b. . . . 69
Microscopical picture of the lymphadenitis . . . 70
General pattern . . . 70
The epithelioid cells . . . 72
The giant cells . . . 73
The inclusion bodies . . . 75
The asteroid body . . . 76
The Schaumann body . . . 77
Regressive changes . . . 80
Caseous necrosis . . . 80
Fibrillar (fibrinoid) necrosis . . . 80
Perifocal inflammatory reaction . . . 82
Indurative changes . . . 83
Vascular lesions . . . 85
Bacterial findings . . . 85

Chapter 9. Series II. Lymph nodes without bacilli. Lymphogranulomatosis benigna . . . 95
Age and sex distribution . . . 95
Clinical picture . . . 95
Clinical relationship to classical tuberculosis . . . 98
Microscopical picture of the lymphadenitis . . . 100
General pattern . . . 100
The epithelioid cells . . . 102
The giant cells . . . 102
The inclusion bodies . . . 103
The Schaumann body . . . 103
The asteroid body . . . 105
Regressive changes . . . 112
Caseous necrosis . . . 112
Fibrillar (fibrinoid) necrosis . . . 113
Perifocal inflammatory reaction . . . 114
Indurative changes . . . 116
Vascular lesions . . . 117
Etiological investigations . . . 120

Chapter 10. General discussion and conclusions . . . 121

Summary . . . 126

Case reports . . . 132

References . . . 175

Introduction

> "The pathological changes are merely one side of a problem, of which the other side is furnished by the clinical picture. Each throws light upon the other, and neither is complete by itself." (William Boyd, 1938)

Many research workers have held that the term *lymphogranulomatosis benigna* (l.b.) represents a clinical rather than a histopathological entity. In fact, as will be shown later, it was for the most part clinical observations which led to the recognition of the syndrome which was described by Schaumann (1914) as lymphogranuloma benignum. The symptomatology of the new syndrome was clearcut but, from a histopathological point of view, it seemed to be extremely ill-defined. Thus, in Schaumann's work there was no discussion of its relationship to certain microscopically similar lesions which, long before that time, had been described under various names by German pathologists and which they had considered to be tuberculous in spite of their differences from the picture of classical tuberculosis. The best known of these conditions, which the German literature usually groups together under the heading *atypical tuberculosis*, is the affection of the lymph nodes described by Ziegler (1890) under the name of *large-celled hyperplasia*. The question of the relationship between l.b. and the Ziegler form of tuberculosis has been brought to the fore by many workers, especially since it became clear that l.b. is often manifested simply as an affection of the lymph nodes. Different views have been expressed. Some, who believe that l.b. is a nontuberculous condition, maintain that it is quite distinct from the lesion described by Ziegler. Others, who, for various reasons, believe l.b. to be a tuberculous disease, maintain that there is an intimate connection between the two conditions. Among the proponents of the latter point of view may be mentioned Mylius and Schürmann. In a work published in 1929 entitled "Universelle, sklerosierende, tuberkulöse, grosszellige Hyperplasie, eine besondere Form atypischer Tuberkulose" they described two cases which they identified as l.b. on account of the symptomatology. In one of these cases tubercle bacilli were demonstrated. As a result of this finding, and because of the similarity of the microscopical picture to that of the lymph nodes described by Ziegler, they considered that their cases represented a generalised form of this condition. According to Vogt (1950) this represented a bridging of the gap, morphologically, between l.b. and tuberculosis.

The problem of the relationship between l.b. and tuberculosis can naturally be approached from many directions. Considering the large number of small publications as well as voluminous monographs (Kiss-

meyer, 1932; Pautrier, 1940; Gravesen, 1942; Dressler, 1942; Leitner, 1942; Schmid, 1951) discussing this problem, it is surprising that, up till now, only one investigator, namely Vogt (1950), has tried to work it out on the basis of extensive pathological studies. After analysing 9 postmortem cases of his own, and 55 described in the literature, he came to the conclusion that l.b. is a tuberculous condition. He based this opinion on two circumstances. One was the great similarity between l.b. and certain forms of ordinary productive tuberculosis as regards morphology and localisation. The other was the common occurrence in l.b. of calcified tuberculous primary foci and old secondary foci which often lay close to the lesions of l.b. He also pointed out that the facts that l.b. often changes into tuberculosis, that tubercle bacilli are not seldom found in the lesions and that the tuberculin reaction is often weak or negative suggest that the disease is of tuberculous nature.

The present investigation was done in order to come to a decision regarding the relationship between l.b. and the Ziegler form of tuberculosis. A large series of lymph nodes showing a fairly similar tuberculoid microscopical appearance was used for the study. The nodes were divided into two series, the ones with and the ones without acid-fast rods. The first of this series obviously represented the Ziegler form of tuberculosis and the second l.b. The two series were compared from several points of view in order to determine the relationship between them. It was also attempted to facilitate the microscopical differentiation between them and to come to a conclusion in regard to the cause of l.b., still the central problem in all discussion on this disease.

CHAPTER I

History

According to Hunter (1936), the disease nowadays generally referred to as l.b. was first described by Jonathan Hutchinson in 1875 in his *Illustrations of Clinical Surgery*. His case was that of a patient with "peculiar purplish, raised lesions on the front of the legs, on the fingers, and on one forearm, which were irregular in size and shape, possessed sharp margins and smooth surfaces, and were neither tender nor painful. Associated with this there was brawny oedematous swelling of one finger" (Hunter, 1936). Hutchinson called this affection *Mortimer's malady*, this being the patient's name. However, no histological examination was performed.

In 1889, a case of what appears to be the same morbid condition was again described, this time by Besnier, the French investigator. His case was that of a man of 34 years of age who had skin lesions mainly on the face. The nose was enlarged and deformed, the skin cyanotically discoloured owing to numerous telangiectases, the orifices of the sebaceous glands were dilated, and there were necrobiotic erosions round the nostrils. The patient also had fungous synovites symmetrically in both hands. Since, in Besnier's opinion, both the skin lesions and the synovites were symptoms of one and the same disease, and considering that he regarded the latter as definitely tuberculous, the name *lupus pernio* was chosen, resembling, as it did, perniones, i.e. chillblains. As a synonym, the term *lupus asphyxique* was suggested. No microscopic examination was made in Besnier's case either.

Tenneson, in 1892, described a case similar to those reported by Hutchinson and Besnier. His case was that of a man of 46 years of age, with reddish-violet swellings of the skin situated symmetrically on the nose and cheeks. Similar lesions were also seen on the chin and ears. The finger joints were swollen and deformed. Numerous teleangiectases were noticed in the affected skin areas, but no tubercles. The microscopic examination in this case was performed by Quinquaud who speaks of "une prédominance excessive des cellules géantes". No bacilli were discovered in the piece of skin examined. No mention was made of any caseous necrosis. Summing up, Quinquaud writes as follows: "Ces lésions sont celles d'un lupus, mais d'un lupus à caractères

histologiques particuliers, qu'on pourra définer anatomiquement: lupus à forme myxomateuse et œdémateuse." His description however does not give a clear picture of the microscopic character of the lesions.

In 1899, this disease again came to the fore in the literature thanks to an excellent report by Caesar Boeck, the Norwegian scientist. In six papers dated 1899, 1900, 1904, 1905, and 1916, Boeck presented the results of his clinical, morbid anatomical and bacteriological studies of the condition which he then believed to be describing for the first time. Although his first publication merely mentions one case of that affection, Boeck was able, during the following five years, to diagnose another nine cases. This indicated that the disease was by no means so rare as would appear, perhaps, from his first report.

Boeck's contribution does not, as he himself thought, consist in the definition of a previously unknown morbid condition, for, as stated earlier, the same disease had probably already been described by the time of Boeck's first publication. On the other hand, it was Boeck who established that the disease was not confined to the skin but, in all probability, affected other parts of the body. This opinion of his, as to the extensive nature of the disease, is suggested even in his first publication of 1899, and is clearly stated in his paper of 1905. In the latter, he points out the occurrence of changes in the mucous membranes, particularly those of the nose, as well as of a more or less general swelling of the lymph nodes. He furthermore assumed, on rather vague grounds, that the disease manifested itself in the lungs ("die Bronchialschleimhaut war in zwei meiner Fälle affiziert"). Boeck was also the first to demonstrate that the large mononuclear cells in the blood of patients suffering from the disease described by him are often increased in number. In addition, a detailed account of the morbid histology of the condition was given by Boeck. It is so accurate and complete that it has not, for the most part, been superseded.

Boeck gave both clinical and morbid histological reasons for believing that the cases he reported represented a disease *per se*. He stated (1905) that "das Auftreten des krankhaften Prozesses in kleinen miliären Foci, die überall die verschiedenen Ausschlagsformen konstituieren, und auch immer in denselben, jedenfalls mittelst der Diaskopie, nachgewiesen werden können" was clinically pathognomonic of the skin affection. He considered that typical cases showed definite lesions in the mucous membranes and lymph nodes without any tendency to disintegration and suppuration in the latter. Also the morbid histology seemed to him to be distinctive. He writes, in 1900, as follows: "A first glance into the microscope was surprising. The picture, like the clinical one, strangely enough lacked any resemblance to other skin affections whose histologic conditions I had been in a position to examine." The peculiarity of the histologic picture of the disease lay, according to Boeck, in the occurrence in the skin of compact, sharply delimited foci,

consisting of epithelioid cells and, with the exception of one case, the absence of caseous necrosis. It was, apparently, this last feature which first suggested to Boeck that the disease was not of a tuberculous nature. Furthermore, the granulomata were not surrounded by leucocytes, as are those in tuberculosis. He also considered the perivascular localisation of the foci of epithelioid cells as characteristic of the process. He gave a striking description of how the vessels, when cut lengthwise, were seen surrounded by "cylindrical tumour masses" and interpreted this as evidence of the lesions originating in the perivascular lymph spaces. He found giant cells in the foci and described them as "sarcomatous" in his first paper. Gradually he changes his opinion on that point and in his paper of 1905 he spoke of genuine Langhans giant cells. Another characteristic feature of the histopathology of the disease described by Boeck was the complete disintegration and loss of the elastic fibres in the skin affected by the morbid process. In his opinion, the histological changes were, on the whole, extremely characteristic. He writes as follows (1905): "Mikroskopisch sind diese scharf begrenzten, kleinen Foci, wie ich in meinen früheren Arbeiten besonders betont habe, in dem Grade eigentümlich, dass etwas vollkommen ähnliches kaum sonst in der ganzen Pathologie der Haut vorkommt, und dass ein einziger Blick ins Mikroskop mit schwacher Vergrösserung hinlänglich ist, um die Diagnose sofort zu machen." In another connection, he maintains: "Wenn ein Fall diagnostische Schwierigkeiten bereiten sollte, wird eine mikroskopische Untersuchung sofort jeden Zweifel entfernen können."

As to Boeck's conception of the nature of this disease, as described by him in his first publication, he expressed the opinion that the affection "histologically may be said mostly to resemble sarcomas, but also the pseudoleukemic tumour formations in the skin reported by Arning and Max Joseph". On account of the probable relation of this affection to sarcomas, and owing to its apparently benign nature, he at first (1899) called it *multiple benign sarcoid.* However, he soon abandoned this conception of the neoplastic nature of the disease. As early as in 1905, he maintained that there could hardly be any question of a neoplastic disease "sondern eher eine entzündliche Wucherung des Bindegewebes". His arguments concerning the etiology of the disease, like many other points in his works, are still valid, and are sometimes marked by an almost prophetic clear-sightedness. Thus, in the paper published in 1900 in honour of Kaposi, he writes: "Woher der Krankheitserreger stammt und welcher Natur er sein mag, ist bis jetzt nicht aufgeklärt. Im kranken Hautgewebe ist es mir nicht gelungen ihn zu entdecken. Eine nähere Untersuchung der Lymphdrüsen wäre vielleicht speziell erwünscht. Es wäre ja denkbar, dass, wenn es sich um eine Infektion handelte, der Eindringling in den Lymphdrüsen zu Hause war und von hier aus die Ernährungs- und Gewebssäfte vergiftete."

However, in his investigations of the etiology of this disease, Boeck (1905) made an observation that was to bring him to a more definite conception of the nature of the condition. Microscopic examination of the nasal mucosa of a patient with multiple benign sarcoid revealed the presence of acid-fast rods indistinguishable from tubercle bacilli as far as their morphology and staining properties were concerned. In order to study the pathogenic properties of these bacilli, he inoculated a fragment of the patient's nasal mucous membrane subcutaneously into the back of a young guinea pig. Fairly soon the animal manifested an enlargement of the axillary lymph nodes. Three months after the inoculation, it was killed and a tuberculous abscess, the size of a pea, was found at the place of inoculation, as well as tuberculous changes in the enlarged lymph nodes of the axillae. Acid-fast rods were seen in the granulomas with the same morphology and staining properties as in the specimens from the mucous membrane of the patient's nose. However, it was noted that all the internal organs of the animal were free from tuberculous changes. In actual fact, this guinea pig test represents the first of a series of more or less atypical tests reported by a number of investigators. These guinea pig tests are atypical in that some animals disclosed only a primary complex, as in Boeck's case, others did not die of generalised tuberculosis until an unusually long time after the inoculation. On the basis of his observation, Boeck (1905) suggested that the disease described by him was due to tubercle bacilli "von wenig giftigen Eigenschaften", and therefore changed the name of the disease to "*benign miliary lupoid*".

Boeck's works attracted a great deal of interest, and in a short while several reports of cases of this disease were published in different parts of the world. Forchhammer (1901) described the affection from Denmark, Gottheil (1902) from the USA and Hallopeau and Eck (1902) from France. In all these cases the skin lesions dominated the clinical picture. The case reported by Hallopeau and Eck was successively diagnosed as lupus erythematosus, lupus tuberculosis, syphilis and lepra before it became clear that it was a case of the disease described by Boeck. This seemed to Boeck (1905) to prove the necessity "dass dieses äusserst scharf charakterisierte Krankheitsbild aufgestellt, näher studiert und allgemein bekannt wird — ganz unabhängig davon, ob es sich um eine Form der Tuberkulose handelt oder nicht".

The term benign miliary lupoid was soon extended to cover a wider range of conditions; Kreibich (1904) and Morosof (1908) reported a case with radiographic changes in the bones. A few years later, Rieder (1910) gave an account of two carefully investigated cases of the disease. The typical skeletal changes manifested in them were, in his opinion, of a tuberculous nature. However, no histological examination was performed. His report is also noteworthy for the fact that one of his cases is probably the first reported case of miliary lupoid in a child.

Zieler's (1909) observation that the disease described as lupus pernio by Besnier is identical with the miliary lupoid of Boeck was an important step forward. Thanks to him, the literature has no doubt been spared many unnecessary differential-diagnostic speculations on the relation between the two affections which are, in fact, identical.

The year 1909 marks an important date in the history of l.b. in another respect also. In that year the Danish ophthalmologist Heerfordt gave a description of a symptom complex involving chronic iridocyclitis combined with bilateral parotitis and, sometimes, also facial paralysis. He found at least two similar cases in the literature which, together with his owns, seemed to him to represent a clinically well-defined disease to which he gave the name of *febris uveoparotidea subchronica.* This morbid condition is also characterised by a protracted course and a subfebrile temperature of long duration. Heerfordt considered that the symptoms from the eyes and parotids were due to inflammatory changes localised primarily to these organs, while the nervous symptoms were secondary and caused by toxins. In discussing the relation of this syndrome to known diesases, he suggested, as a first consideration, the possibility of a connection with parotitis epidemica. However, he also considered the possibility of its being an infection due to some unknown pathogen. No microscopical examination was performed in any of these cases. If it had been undertaken, Heerfordt would surely have considered the possibility of a specific infection, and the relation of the disease to Boeck's benign miliary lupoid, which is not mentioned in his work.

In 1914, Schaumann's excellent work, *Sur le lupus pernio,* was awarded the French Zambaco prize. It both confirmed the accuracy of Zieler's statement that the complaints described by Besnier and Boeck were identical, and proved that lupus pernio was, primarily, a disease of the lymphoid system and, probably, also widely distributed in the body. Schaumann pointed to certain lesions other than those of the skin as characteristic of the disease. These were a multiple enlargement of the lymph nodes (already described by Boeck), a hitherto unrecognised but characteristic radiographic appearance of the lungs which showed bilateral flocculation and striation especially in the perihilar regions, bone lesions (previously described by Morosof, see above), enlargement of the liver and spleen, and a negative tuberculin reaction. Schaumann not only recorded the histology of the skin lesions, but also examined extirpated enlarged lymph nodes in which he found new-formed tissue with the same histologic characteristics as in lupus pernio of the skin. Microscopic examination of apparently unaffected tonsils revealed the presence of the same granulomatous process as in the skin and lymph nodes. Owing to lack of autopsy material he was unable to prove, in 1914, that the pulmonary and skeletal changes observed radiographically, and the enlargement of the liver and spleen,

were caused by lesions having the same histological characteristics as those in the skin and lymph nodes. The fact that such changes often occur in lupus pernio simultaneously, with enlargement of the lymph nodes, however, strongly suggested to Schaumann that the pulmonary and skeletal changes observed radiographically, as well as the enlargement of the liver and spleen, were manifestations of the same morbid process in different situations.

Although, in Schaumann's opinion, the histological changes in lupus pernio "n'est pas caractéristique seulement de la tuberculose mais aussi de plusieurs autres infections chroniques, telles que la sporotrichose et la syphilis", he considered it worth while to try to establish whether the tubercle bacillus might be the cause of the disease. He therefore inoculated a number of guinea pigs with the skin, lymph nodes and blood taken from patients suffering from lupus pernio. However, the animals showed no signs of tuberculosis. Neither did he succeed in finding any other cause of the disease. Accordingly, because of the unknown etiology, and the localisation of the affection mainly to the lymphoid system, as well as owing to the favourable prognosis of the disease, Schaumann chose the name of lymphogranuloma benignum which was later changed to the present lymphogranulomatosis benigna.

With all due respect for Schaumann's contribution, his definition of the disease must, from various points of view, be regarded as misleading, both in the main word and the attribute benigna. The term lymphogranuloma is unsuitable because the process is not confined to the lymphoid system. Further, the added benignum was later admitted by Schaumann himself to be unsuitable. In 1937, he pointed out that "the prognosis is by no means favourable and the benign character of the disease which is stated in its name should only be acknowledged as relative".

The accuracy of Schaumann's observations in 1914 was soon confirmed by a number of other scientists, the most important publication being that of Kuznitzky and Bittorf in 1915. They arrived at the same conclusions, independently of Schaumann's work.

Thus, Schaumann's investigation in 1914 clearly showed that the lesions of l.b. are widely distributed in the body. However, it gradually emerged that the definition of the condition was still too narrow. By the middle of the nineteen-thirties, thanks mainly to the work of With (1936) and Waldenström (1936), it was established that the uveoparotitis described by Heerfordt is a form of l.b.

After the essential features of clinical and morbid anatomical appearance of l.b. had become known, the question of the etiology of the disease attracted increasing attention. The French school of dermatology contended that it is not of a tuberculous nature, while several German dermatologists and, in particular, German pathologists, were of a reverse opinion. The term lymphogranulomatosis benigna has therefore

not been accepted in the German literature, nor has the undoubtedly inadequate term sarcoidosis prevalent in American works. In fact, the majority of German authors show a tendency even to call the disease by names suggesting that it is an atypical form of tuberculosis. Thus, as already stated, Mylius and Schürmann (1929), in describing two cases of a disease which seems to be identical with l.b., chose the title "Universelle, sklerosierende, tuberkulöse, grosszellige Hyperplasie". The same may be said of the five cases reported by Hantschmann (1930), in a work entitled "Über torpide Formen disseminierter Tuberkulose". These two terms have also been stated by later investigators to be synonymous with l.b. (Freund, 1932; Lindau and Löwegren, 1940, and others). The histological appearance of the affection described by Mylius and Schürmann is definitely recorded in the following way: "Der histologische Baustein ist die nicht verkäsende, zumeist in submiliaren Herden auftretende tuberkulöse, grosszellige Hyperplasie mit der hyalinen Sklerosierung als der schlechthin einzigen Form von regressiver Metamorphose." It was the histological character of the lesions as well as the finding of tubercle bacilli in one of the observed cases which convinced these authors that the disease is a form of tuberculosis.

As may be seen from the above résumé, the definition of the morbid condition classified by Besnier as lupus pernio has been successively widened. The fact that l.b. is nowadays considered to be a generalised disease indicates that almost any organ can be affected, as recently observed (Vogt, 1950, and others). The development of the term lupus pernio to refer to a large symptom complex of clinical significance has, as previously demonstrated, taken place successively and the phrase once coined by Harvey Cushing that "discovery is a process, not an event", applies with special force to l.b. The most important contributions to this course of development have undoubtedly been made by Boeck and Schaumann, and the disease has therefore rightly also been called *Morbus Boeck-Schaumann.*

CHAPTER 2

Clinical Observations

As far as can be seen from the literature l.b. occurs throughout the world. In the Western countries it is by no means rare and, as Dressler (1942), among others, has pointed out, it is certainly more widespread than one would normally suppose, because it often runs its course almost without symptoms. The great increase in radiographic screening which has taken place during recent years has therefore led to the discovery of an unexpectedly large number of cases of l.b. which would probably never have been diagnosed otherwise (Dressler, 1942).

It is thus impossible to give accurate figures for the incidence of l.b. in any population without carefully investigating it for the presence of asymptomatic forms of the disease. The figure of 6.6 per million for the incidence of l.b. given by the British worker Robb-Smith (1947) only takes account of cases presenting symptoms and is therefore certainly too low.

Several authors including Pautrier (1940) and Gravesen (1942) have tried to maintain that l.b. is particularly common in the Scandinavian countries. It is certainly true that the clinical contributions to our knowledge of this disease were predominantly derived from these countries during the whole of the 1930's and well into the 1940's. This, of course, does not necessarily mean that the disease is especially widespread in the countries concerned. It may be explained, at least in part, by the fact that a knowledge of the various manifestations of the condition was more widespread in Scandinavia at that time, a state of affairs for which Schaumann's investigations might well be responsible. The part played by the Scandinavian literature in spreading knowledge about l.b. has, in recent years, been overshadowed by that of the Swiss. For reasons similar to those given above, this need not necessarily mean that l.b. has become commoner in Switzerland of recent years but may easily be due to the great interest which has been taken in the disease in that country since the Swiss worker Leiter published his monograph on l.b. in 1942.

Thus, although the early Scandinavian interest in l.b. seems able to explain to a large part why the disease has come to be called "the

Scandinavian disease" (Pautrier, 1940) it is still impossible to exclude the possibility that the condition really is, and has been, more prevalent in Scandinavia and Switzerland than in other countries. Some authors, believing l.b. to be a tuberculous condition, have expressed the opinion that it represents a new form of defence by the organism against tuberculous infection and that the reason for its appearance is "eine Durchseuchung der gesamten Bevölkerung" (Bergmann, 1939). The improved immunological status of the population as regards tuberculosis would, according to this view, favour the increased incidence of l.b.

The question as to whether l.b. is commoner among negroes than among white people has given rise to lively discussion. Even though most authors (Thomas, 1943; Reisner, 1944; Irgang, 1947; Rosenthal and Feigin, 1948; Cone, 1948) say that they have the impression that it is, it is only in recent years that attempts have been made to study the problem objectively. Using a series of 350 cases of l.b. Michael, Cole, Beeson and Olson (1950) calculated that the disease is about 10 times as common among negroes as among white people.

Some authors (Schaumann, 1936; Cone, 1948, and others) have asserted that l.b. is commoner among country people than among townspeople and, according to Schaumann, the skin lesions in particular appear more often among country people or people who have spent a large part of their lives in the country. However, this supposed greater prevalence of l.b. among country people has not been confirmed by later authors. For example, in Gravesen's (1942) series of 150 cases 52 patients were occupied on the land while 98 lived in towns. The work of Vosbein and Bonnevie (1940) also contradicts the view that the greater number of patients with l.b. come from country districts.

L.b. affects people of all ages but is commonest about the age of 30. Thus, according to Robb-Smith (1947), the mean age of onset is 32 years, according to Löfgren and Lundbäck (1952) the condition has its highest frequency between the ages of 25 and 29 years. It is rare in children and old people. Rieder (1910), Martenstein (1924), Roos (1938), Buwalda (1946), Cone (1948), and Schmid (1949), among others, have described the condition in children. Good reviews of the literature are to be found in the papers of Roos and Schmid. According to this last author 97 cases of l.b. in children had been published by 1948. As far as its occurrence in old people is concerned Boeck (1910) described a case in a woman of 71. Up till then the disease had never been seen in such an old person but it is now known to occur in even older people.

L.b. would appear to be rather commoner among women that among men. In Gravesen's (1942) collection of previously published cases, 734 in all, the sex was given in 679. Of these 387 were women and 292 men. In his own series too, women were more numerous than men.

One strange feature is that, in women, the first symptom of l.b. often appears during pregnancy or lactation. This was pointed out by Gravesen

as early as 1942. Törnell (1946) and Löfgren and Lundbäck (1952) made the same observation in respect of the so-called BHL syndrome which is clearly closely related to l.b. (see Chap. 3).

It is worthy of note that l.b. quite often occurs in members of the same family. Thus Robinson and Hahn (1947) found the disease in two of the three children in a negro family. The course was similar in both cases. In another negro family only five of the ten children could be examined, but three of these were found to have the disease while the diagnosis of l.b. seemed probable in a fourth. One child was thought to have died of the disease previously. Two of the sick children died of tuberculosis. Among the white races, too, a familial incidence has been noticed. Thus Jacobsen (1936) observed the disease in two sisters aged 8 and 13 who both died later of tuberculosis, Dressler (1938) in a brother and sister aged 25 and 28 respectively, Dressler (1939) in two brothers aged 19 and 24, Bergmann (1939) in a sister and brother aged 19 and 20 respectively, and Leitner (1949) in another brother and sister aged 22 and 25. The last-named author has also seen the disease in a father and son. Other cases of the familial occurrence of l.b. have been described (MacCormac, 1940, and others). The fact that l.b. quite often attacks brothers and sisters has led some authors (Dressler, 1942; Leitner, 1942), who, for different reasons, believe l.b. to be of tuberculous origin, to adopt the view that it is a form of tuberculosis in which the atypical course is determined by constitutional factors.

As has been pointed out, l.b. is a disease with a marked tendency to affect many organs. This however, does not mean that many parts of the body are affected from the start. On the contrary, the progress of the disease is usually characterised by the appearance of new symptoms one after another, often over periods of years. Gravesen (1942) gives the duration of the disease as 8–12 years but, as Vogt (1950) and others have pointed out, there is reason to suppose that if the length of the disease is judged by its clinical manifestations it will be estimated at far less than its real length.

Although, if observed for long periods, cases of l.b. usually show more than one symptom, some cases have been described in which only one symptom was present over periods of many years (Bergmann, 1939; Gravesen, 1942; van Buchem, 1946). Probably, this is partly because the disease does not spread from the site where it originates, which is believed by many to be the lungs and hilar lymph nodes (Dressler, 1942; Longcope and Pierson, 1937; Löfgren and Lundbäck, 1952); and partly because its spread to the viscera such as the abdominal lymph nodes, liver, spleen and kidneys cannot be detected clinically. In discussing the frequency of skin lesions in l.b. Schaumann discussed this possibility as early as 1914: "One cannot entirely exclude the possibility of the disease often pursuing a concealed existence in the lymphatic glands and the internal organs ... ." Examination of series of cases which have

been investigated both clinically and patho-anatomically shows that this supposition is correct.

According to Robb-Smith (1947) a series of cases which have been investigated clinically shows the following distribution of lesions in the various organs: generalised lymph node enlargement, 74%; pulmonary change, 37%; splenomegaly, 12%; salivary gland involvement, 7%; and bone involvement, 5%. In the review of Vogt (1950), based on 55 cases reported in the literature and 9 autopsy cases of his own, lesions were found as follows:

1. Lymph nodes	58 times	9. Other bones	8 times
2. Lungs	44 ,,	10. Pleura	8 ,,
3. Spleen	44 ,,	11. Brain	6 ,,
4. Liver	42 ,,	12. Tonsils	6 ,,
5. Kidneys	18 ,,	13. Pericardium	5 ,,
6. Myocardium	17 ,,	14. Testes	4 ,,
7. Skin	16 ,,	15. Endocardium	4 ,,
8. Bone marrow in fingers and toes	9 ,,	16. Peritoneum	3 ,,
		17. Thyroid gland	3 ,,

Lesions were also found on two occasions in each of the following sites: epicardium, trachea, diaphragm, parotids, digestive tract, pancreas, retina, iris, and spinal cord; and once in the following: meninges, eyelid, optic nerve, ciliary body, hypophysis, epididymis, nasal mucosa, and adrenals.

The considerably greater frequency of changes in the internal organs in the autopsy cases is probably due, to a certain extent, to the fact that the autopsy cases are those in which the disease has become most widely disseminated within the organism. However, the greater part of the discrepancy seems to be caused by the previously described tendency of l.b. to progress from organ to organ without any apparent system. The fact that changes in the skin and eyes are commoner in clinical than in autopsy series is easily explained because it is just these manifestations of the disease which lead the patient to consult the physician.

Pulmonary Symptoms

In describing the pulmonary manifestations of l.b. it seems suitable to follow Dressler (1942) and to deal not only with the changes in the actual lung parenchyma but to include lesions of the hilar lymph nodes and the other intra-thoracic lymph nodes which are intimately connected with them as well as the pleurae.

As early as 1922 Schaumann suggested the possibility that the lungs might be the portal of entry of l.b. into the organism. If this is really the case it must be expected that the lungs are the part of the body most often affected. Several other authors including Pinner (1938), Ustvedt (1939), Gravesen (1940) and Löfgren and Lundbäck (1952) are also of

this opinion. Radiological investigation of the lungs certainly gives no support to this hypothesis in the form of showing parenchymatous changes primary to the hilar node enlargement which usually seems to usher in the pulmonary changes. This, however, does not exclude the possibility that a primary lesion was once present in the pulmonary parenchyma but had disappeared by the time the swelling of the hilar nodes had appeared. There would seem to be no justification for joining Gravesen (1942) in believing that the affection of the hilar nodes is simply part and parcel of a more generalised attack on the lymphoid tissues, for experience has shown that l.b. is sometimes localised to the lung parenchyma and hilar nodes alone or to them and the other mediastinal nodes (Dressler, 1942, and others).

Different changes in the lungs in l.b. used to be referred to as "Boeck's disease of the lungs" or "Boeck's disease of the hilar nodes" but it has gradually become clear that these forms are really only stages in the development of the pulmonary process (Gravesen, 1942; Thomas, 1943, and others).

The *first* stage in the development of the pulmonary lesions is characterised by the appearance of bilateral hilar adenitis. On the radiograph these appear as large, relatively symmetrical opacities at the hili, having rounded, oval or sometimes bi- or polycyclic margins. Van Buchem (1946) has aptly called these nodes "potato nodes". The most important differential diagnosis in this stage is from malignant lymphogranulomatosis and classical tuberculosis. As concerns the latter disease, it would appear that, in certain cases, primary tuberculosis of the lungs is associated with bilateral hilar adenitis. Thus, in a series of 178 cases of erythema nodosum Löfgren (1946) found bilateral hilar lymphomata as a primary tuberculous symptom in about 5 per cent. The question of the extent to which post-primary tuberculosis manifests itself in the form of bilateral hilar adenitis does not seem to have been answered.

The *second* stage, the onset of which is quite often accompanied by a diminution in the hilar shadows, is characterised by the appearance of more or less fan-shaped opacities composed of miliary granules and radiating from each hilus into the lung parenchyma. The term "fan-shaped" is intended to indicate that the apical and basal regions are usually unaffected. The radiographic picture at this stage resembles that of chronic miliary tuberculosis (S. Berg, 1940), silicosis (Bruce and Wassén, 1940; Gravesen, 1942), lymphogranulomatosis maligna (Bruce and Wassén, 1940), and certain tropical mycoses (e.g. coccidioidomycosis) and moniliasis (Törnell, 1946, 1949). The parenchymal opacities nearest the hilus are often so confluent that it is hard to make out how far the hilar adenitis has regressed and how much remains.

In the *third* stage the miliary shadows disappear more or less completely and sometimes give place to a "bushy" striation radiating from

the hilus. In some cases this may remain for many years. The swelling of the hilar nodes has generally vanished by the third stage too.

Although the pulmonary lesions in most cases of l.b. pass through the three stages just outlined this is not always so. The process may be arrested in, for example, the first stage and thus only manifest itself in the form of bilateral hilar adenitis.

In their first two stages the pulmonary changes in l.b. do not often give rise to subjective symptoms. Pinner (1938) maintains that "the spectacular discrepancy between the massive anatomical involvement and the paucity of respiratory symptoms and physical signs is a distinct help in the diagnosis of pulmonary sarcoid". As a result of their asymptomatic course, the pulmonary changes in these two stages often pass unnoticed (Bergmann, 1939). In some cases, however, there are severe symptoms in the form of cough and dyspnoea. In one of the two cases described by Mylius and Schürmann (1929) the dyspnoea was so severe that operation had to be performed, about 600 g of affected lymph node tissue being removed from the hilar regions. In a couple of cases of l.b. reported by Bruce and Wassén (1940) severe attacks of coughing occurred which put a great strain on the patient. These authors maintain that "severe coughing attacks might constitute an early symptom of the disease at a time when the pulmonary lesions have not yet developed but when the conditions in the thorax are predominated by a swelling of the lymph nodes in the hilar regions". Finally, Thomas (1943) reported a case of l.b. in which the patient died of a massive pulmonary infarction caused by pressure from tremendous enlarged mediastinal lymph nodes.

However, in spite of the examples given above, it may still be stated that the pulmonary changes in their first two stages very rarely give rise to much in the way of symptoms. The position is quite the reverse in the third stage. As a result of the induration which sets in at this stage there is not seldom dyspnoea, increasing with the passage of years. This, like the cyanosis which appears at this stage, may be attributed to impairment of the pulmonary circulation with hypertrophy of the heart and pulmonary stasis. A common cause of death in these patients is therefore oedema of the lungs from chronic cor pulmonale (Ustvedt, 1948, and others).

As Bruce and Wassén (1940) pointed out, pleural affections presenting themselves clinically are rare in l.b. Cases where there was exudative pleurisy have, however, been described (Sundelin, 1933; Nielsen, 1934). On the other hand, autopsy experience shows that adhesive pleurisy is not at all uncommon among patients with l.b. (Mylius and Schürmann, 1929; Schaumann 1936; Vogt, 1950, and others). The fact that the traces of past pleurisy are to be found in patients dying of l.b. should not, of course, be taken to indicate that they are due to that disease without other evidence.

Lymphadenopathy

It used to be held that the skin lesions were the commonest manifestation of l.b. and cases of "lupus pernio sine pernio" were reported as rare exceptions from this rule, but it has gradually become clear that the peripheral lymph nodes are affected considerably more often than the skin and that, after the lungs and hilar nodes, they are probably the organs most frequently attacked by l.b.

The affection of the peripheral lymph nodes usually manifests itself as swelling which is, as a rule, not tender. As Schauman (1936), among others, has pointed out, affection of the lymph nodes does not always show itself as enlargement.

The enlargement of the lymph nodes may either be general or may be confined to one or more groups, e.g. the occipital nodes of the lymph nodes of the neck. Generalised enlargement of the lymph nodes as a symptom of l.b. is relatively rare, however, and in Gravesen's (1942) discussion of the 277 cases described in the literature having enlargement of the peripheral lymph nodes this was only generalised in 24 cases, that is about 9 per cent, while swelling confined to the lymph nodes of the neck occurred in 176 cases, or about 64 per cent. In his own series of 150 cases of l.b. there were 68 in which the peripheral lymph nodes were enlarged and the distribution of sites was as follows:

Nodes of the neck . . .	11	cases
Axillary nodes	23	,,
Cubital ,, ...	10	,,
Inguinal ,, ...	24	,,
Other groups	14	,,

The enlargement of the peripheral nodes is usually moderate. They are relatively seldom larger than 1 cm × 2 cm. They differ in this respect from the visceral nodes (e.g. those of the mediastinum) which are, as already stated, often markedly enlarged.

The peripheral lymph nodes are usually very firm and freely mobile in relation to the skin and the underlying tissues. It is only in exceptional cases that there is periadenitis with fixation of the nodes to the surrounding tissue. Suppuration and fistula formation form no part of the clinical picture.

There are some cases in which the clinical picture arouses a suspicion of l.b. but in which it is hard to find lymph nodes for biopsy. In such cases the method of taking material for biopsy described by Daniels (1949) would appear to be useful. This method involves the excision of adipose tissue from the region between the sternocleidomastoid and scalenus anticus muscles, which, as a rule, contains small lymph nodes connected with the lymphatic system of the mediastinum and often affected by l.b. Using this method Norviit, Carstensen, Odelberg and

Wahlgren (1952) were able to show that in 21 cases, where there was a suspicion of l.b. but no lymph nodes palpable, the diagnosis was supported or confirmed in 15 cases (71 per cent).

Splenic Involvement

Although splenomegaly is seldom detected clinically it is, as was shown in the paper of Vogt (1950) referred to earlier, a common finding at autopsy on cases of l.b. (Schaumann, 1936; Nickerson, 1937; Friedman, 1944; Kay, 1950).

When enlargement of the spleen is observed clinically it is usually moderate; but it can be the dominating symptom as, for example, in the four cases reported by Kay (1950). In one of these the spleen weighed 4800 g.

The affection of the spleen seldom leads to symptoms. In some cases, however, a considerable diminution of thrombocytes with thrombocytopenic purpura has been observed (Jersild, 1938; Berblinger, 1939; Kraus, 1942; Enzer, 1946; Kay, 1950; Bruschi and Howe, 1950; Kunkel and Yesner, 1950).

Hepatic Involvement

The liver is often affected in l.b. Usually, however, the granulomata are inconsiderable both in number and size so that it is a question how far the enlargement of the liver which has been observed by most authors to occur in l.b. (Martenstein, 1924; Kissmeyer 1932; van Buchem, 1946, and others) is really due to the presence of granulomata. As has already been mentioned, the affection of the lungs quite often leads to stasis in the pulmonary circulation. It may well be, therefore, that the enlargement of the liver in l.b. is usually to be considered simply as a manifestation of stasis. This view is supported by the observation made by van Buchem (1946), among others, that the liver may be affected without being enlarged.

Van Beek and Haex (1943), van Buchem and Botman (1943) and van Buchem (1946) have performed aspiration liver biopsy in order to find out how often the liver is affected in l.b. The series contained 4, 8 and 14 cases respectively. Van Beek and Haex found lesions characteristic of the disease in 2 of their cases while in van Buchem and Botman's cases the results of liver biopsy were positive in six (75 per cent) and in van Buchem's the characteristic granuloma tissue was present in 78 per cent. Considering that the tissue obtained by puncture may, in certain cases, not have been representative, these figures must be considered as minima. Scadding and Sherlock (1948) also found characteristic lesions in liver tissue obtained by aspiration biopsy in three cases presenting clinical

manifestations of l.b. In a fourth case, in which similar changes were an incidental finding in liver biopsy, the patient presented no clinical symptoms of l.b. Finally Baird, Bogoch and Fenwick (1950) were able to verify the l.b. diagnosis in three cases by liver biopsy.

The liver and spleen are often both attacked. Thus, the liver was found to be affected in three of the four cases of l.b. with splenomegaly described by Kay (1950) and discussed above. This hepatolienal form of l.b. has sometimes been misdiagnosed as portal thrombosis, especially when both liver and spleen were enlarged.

According to Scadding and Sherlock (1948) the possibility of finding out whether the liver is affected in l.b. by using function tests does not seem to be very great. It is true that van Buchem (1946) found a positive Takata and pathological values in both the Weltman and the galactose tests in two of his patients in whom the presence of granulomata in the liver had been verified by biopsy, but in most of the patients showing these changes in the liver the function tests showed no abnormality.

Skin Lesions

As has already been pointed out, skin lesions were the first part of the l.b. syndrome to be noticed and for a long time held pride of place. As other manifestations of the condition were found to be commoner than the skin lesions these have lost their original status as the cardinal symptom of the syndrome and this has been taken over by the lymphatic and pulmonary changes. Even though they have gradually been found to occupy a relatively minor position in point of frequency, they still arouse great interest from the points of view of differential diagnosis and treatment.

As early as 1904 Kreibich demonstrated that lupus pernio usually begins in the region of the nose. Many observations have supported this view, and later authors have pointed out that the cheeks, lobes of the ears, extensor surfaces of the arms, buttocks and shins are also the sites of predilection for the cutaneous manifestations of the disease. The parts of the skin just mentioned have for long been thought to be relatively poorly supplied with blood vessels (Kreibich, 1904; Gravesen, 1942). The dermatologists have expressed it by saying that lupus pernio has a predilection for the northern or cold aspects of the body.

Boeck (1905) had already classificed the skin lesions of l.b. into three clinically distinct categories—one in which the nodules are small, one in which they are large, and one in which the lesions take the form of a diffuse superficial infiltration. The common feature of these clinical categories is the presence of many miliary foci "die wir immer mikroskopisch und auf einem gewissen Stadium auch immer klinisch nachweisen können" (Boeck, 1905). Under pressure with glass these foci appear

as extremely fine yellowish brown nodules. Boeck's three categories are still apposite but three further categories have been added. The first is the erythrodermic form (Schaumann, 1920, 1934; Pautrier, 1932; Hellerström, 1935; Nordin, 1940), the connection of which with l.b. seems to be undisputed; the second is Darier-Roussy's subcutaneous sarcoid; and the third the rare angio-lupoid (Broque-Pautrier). It should, however, be pointed out that the connection of the last two of these categories with l.b. is doubted by many authors (Bour, 1942, and others).

A characteristic feature of the skin lesions of l.b., as of most of the other manifestations of the disease, is their chronicity. In a couple of cases described by MacCormac (1940) they had persisted for about 40 years.

Febris uveoparotidea subchronica (Heerfordt)

Even if the previously described Heerfordt's syndrome is relatively uncommon—it occurred in only seven patients in Gravesen's (1942) series comprising 150 cases of l.b.—there are nevertheless numerous reports of uveoparotitis as a symptom of l.b. (F. Berg, 1923; Waldenström, 1936; Adler, 1936; Österberg, 1939; Lindau and Löwegren, 1940, and others). A comprehensive and critical review of the literature has been given by Garland and Thompson (1933). There are also numerous descriptions of cases of l.b. in which either the eyes or the parotids were affected.

The *iridocyclitis* occurring in this syndrome is almost always bilateral and extremely disabling in its nature (Essen-Möller, 1941). Thus, it often leads to severe impairment of vision and sometimes to complete blindness. It usually begins acutely or subacutely with photophobia and pain in the eyes. Examination shows ciliary injection, opacity of the cornea, precipitation, hyperemia of the iris and opacities in the lens. According to Rasmussen (1943) two types of changes may be distinguished, namely, a nodulate iritis and iridocyclitis with profuse precipitates. As regards the frequency of the ocular changes, Essen-Möller (1941) believes that 3–5 per cent of all cases of iridocyclitis are due to l.b.

There is a difference of opinion as to whether it is possible to distinguish clinically the eye changes in l.b. from those which are definitely tuberculous. Blegvad (1931), for example, considers that it is possible. According to him the tuberculous nodules in the iris are whitish with a pale yellowish pink tinge and have smooth surfaces, while the nodules in l.b. are reddish yellow and have uneven surfaces. Other authors, for example Österberg (1939), however, consider that "iritis Boeck" cannot be differentiated from tuberculous iritis. Rasmussen (1943) maintains that the eye changes in l.b. remind very much of tuberculous uveitis. Finally, F. Berg (1923) has pointed to the impossibility of distinguishing between the eye changes in l.b. and those of a similar

nature which have been proved to be of tuberculous origin. He maintains that the iridocyclitis in Heerfordt's syndrome very often presents just the picture which has been described as being typical of tuberculosis of the iris. In putting forward his reasons for believing in the tuberculous nature of Heerfordt's syndrome Berg writes: "It is not only those cases in which nodules develop in the iris which, from the point of view of clinical ophthalmology, are clearly to be diagnosed as tuberculous, but the iridocyclitis seen in other cases presents a picture which agrees very well with the clinical picture of tuberculous iridocyclitis. The fact that it is bilateral though there is often a greater or less interval between the onset on the two sides, the profuse precipitate, the marked tendency to the formation of synechiae, the exudation into the lens and the changes in the fundus which appear from time to time are all symptoms which could hardly be included under any known diagnosis except that of tuberculosis. Nor have there been observed any ocular symptoms inconsistent with this diagnosis."

As for the other ocular symptoms of l.b., conjunctival lesions have been described by Boeck (1900), Lutz (1919), Schoeppe (1920), Volk (1922), Igersheimer (1925), Blegvad (1931), Seefelder (1932), and others. Corneal lesions have been described by Seefelder (1932). Lesions in the lachrymal glands in l.b. have been reported by Lund (1938), Ustvedt (1939), and Gravesen (1942). A case of uveoparotitis with perivascular changes in the fundus has been described by v. Bahr (1938).

The *parotitis* is almost always bilateral. It manifests itself as an indolent enlargement of the parotid glands which feel firm and more or less lobulated. The most prominent subjective symptom is usually a certain sensation of dryness in the mouth and dysphagia; these are probably due to diminished secretion of saliva. The swelling of the parotids usually goes down after a few months but may last a long time. In one case reported by Gjessing (1916, 1918) it lasted 13 years.

As is indicated by its name, *fever* forms part of the syndrome. The raised temperature seldom rises above 38° C and generally lasts 2–3 months.

A fourth symptom in Heerfordt's syndrome consists in a bilateral *facial paresis*, usually of the peripheral type. It does not form an essential part of the syndrome but occurs in about half of the patients with uveoparotitis (Michelson, 1939). Most authors regard it as a complication of the parotitis, caused either by direct pressure on the nerve or by a toxic effect.

Bone Lesions

As was stated previously, the bone lesions in l.b. were first described by Kreibich (1904), but did not become generally recognised until the work of Schaumann (1914) and, even more important, that of Jüngling

(1920, 1928). They are usually localised to the phalanges. Radiographically they appear as cyst-like clear areas in the medulla of the bones which have been strikingly described as ticket punch holes. The description "osteitis tuberculosa multiplex cystica" is derived from Jüngling's first paper (1920); however, in his work of 1928 he maintained that the lesions were not cystic and accordingly changed the name to cystoides. The periosteal reaction is usually insignificant. Sequestrum formation is extremely rare. According to Jüngling, there is, as well as this cyst-like type of bony lesion, a diffuse form manifesting itself as a coarsening or sometimes obliteration of the structure of the medulla (lattice markings). Some authors consider this to be an earlier stage of the cystic type. According to Pinner (1938) the bone lesions are chiefly seen in those cases with cutaneous lesions.

The bone lesions, like most of the other manifestations of l.b., are markedly benign in character. They develop slowly, usually without subjective symtoms, though occasionally they cause pain (Volk, 1922). Thus it is extremely rare for the process to break through the cortex and affect the soft tissues. Bony changes leading to deformity, such as are seen in leprosy, have however been observed by Fleischner (1924).

Lesions of the Central Nervous System

Most of the cases of l.b. in which cerebral symptoms have been found have presented the picture of uveoparotitis, and, as has already been pointed out, uni- or bilateral facial paresis forms a part of Heerfordt's syndrome. Other cranial nerves than the seventh can, however, also be affected. Thus, in a case reported by Rothfeld (1930) there was paralysis of the soft palate, a sign of affection of the fifth cranial nerve, and the same was true of Mohn's (1933) patient. Signs of meningitis have been observed in some cases. They take the form of stiffness of the neck (Adler, 1936; Naumann, 1938), positive protein reactions in the cerebrospinal fluid and a rise in its cell count, which is usually only moderate (Adler, 1936; Bergmark, 1936; Waldenström, 1937). Cerebellar symptoms have also been noticed (Bergmark, 1936).

Mental unrest and hallucinations are rare symptoms of l.b. (Bang, 1918; Bergmark, 1936; Roos, 1938; S. Berg, 1940). In the case described by Bergmark the cerebral symptoms started in the form of status lethargicus so that, at first, the diagnosis of epidemic encephalitis seemed probable.

Another symptom of affection of the central nervous system which has been described in l.b. is diabetes insipidus. As early as 1909 Heerfordt observed a transient polyuria in one of his patients with uveoparotitis and, since then, diabetes insipidus has been observed in l.b. by Tillgren (1935), Levin (1935), Flandin, Parat and Poumeau-Delille (1936), Lesné,

Launay and Sée (1936), among others. In Tillgren's case microscopical examination of the hypophysis showed granuloma tissue in the pars intermedia. In a case described by Kraus (1942) the signs of hypophyseal damage included not only diabetes insipidus but also extreme emaciation, atrophy of the thyroid, suprarenal bodies and internal genitalia as well as notable loss of hair. Microscopical examination of the hypophysis showed the granuloma tissue characteristic of l.b. not only in the anterior and posterior lobes but also in the stalk of the hypophysis.

The Tuberculin Reaction

In the three especially carefully investigated cases of l.b. described by Schaumann in 1914 the tuberculin reaction was negative and he believed that the absence of sensitivity to tuberculin was an important diagnostic criterion. Later investigations have shown, however, that insensitivity to tuberculin is by no means necessary to the establishment of the diagnosis of l.b. It is true that a low sensitivity to tuberculin is, in general, characteristic of the disease, but there are numerous exceptions to this rule (Kissmeyer, 1931; Gravesen, 1942; Leitner, 1949; Löfgren and Lundbäck, 1952). Out of 36 cases in which Leitner (1949) performed tuberculin tests 19 gave positive reactions.

In quite a number of l.b. patients the allergy is only seen when rather large doses of tuberculin are used. Bonnevie and With (1937) gave tuberculin intracutaneously to 25 patients and found that 15 of them gave a positive reaction and 10 a negative one when 1 mg was used. In 9 of the cases where the reaction was positive with 1 mg it was negative with 0.01 mg. This shows that one must not assume that the tuberculin reaction is negative in cases of l.b. without trying the effects of much larger doses than are normally used in practice. If the doses used are too large, however, one has to reckon with the possibility of non-specific reactions.

In some cases of l.b. general reactions to tuberculin have been observed in the form of fever (Zieler, 1909; Nobl, 1924, and others). These have sometimes been associated with focal reactions. In a case of uveoparotitis described by Gjessing (1918) the temperature rose to nearly 40° C after injection of 1 mg tuberculin. There were also focal symptoms in the form of reddening of the eyes and increased precipitation. A similar case was reported by Marie (1944). In this case tuberculin testing led to a tremendous exacerbation of the patient's iritis. In a case of l.b. described by Lutz (1919) subcutaneous injection of 2 mg tuberculin led to pains in the skin lesions which became redder than they had been before.

The low sensitivity of patients with l.b. to tuberculin is now thought to be due to a desensitising effect of the disease. The investigations of Bonnevie and With (1937) and Martenstein (1924) show that the number

of negative reactors in a series of cases of l.b. is lower than that in a control series drawn from the population at large, which supports the supposition just made. Another observation tending in this direction is that made, among others, by Törnell (1946) that in cases of l.b. the tuberculin reaction often changes from negative to positive as the disease passes over.

An interesting fact which has been pointed out by Schaumann (1924, 1934) and others is that if a patient with l.b. becomes afflicted with classical tuberculosis his tuberculin reaction, which was formerly negative, will often become strongly positive. It may also be mentioned in this connection that the skin and bone changes sometimes regress or completely disappear under these circumstances (Schaumann, 1936; Bonnevie and With, 1937, and others).

CHAPTER 3

Lymphogranulomatosis Benigna and the Bilateral Hilar Lymphoma Syndrome

In the Scandinavian literature especially, and particularly during the last 10 years, there has been great interest in a syndrome consisting of erythema nodosum, bilateral hilar lymphomas and a low sensitivity to tuberculin which is sometimes accompanied by fever, joint pains, and a raised sedimentation rate. On account of its most constant and impressive feature, the bilateral hilar lymphomas, this syndrome has been called the bilateral hilar lymphoma syndrome (BHL syndrome: Löfgren, 1946, or the bilateral hilar adenitis syndrome (BHA syndrome: Ustvedt, 1948). As may be seen it shows great similarity to l.b. Thus, both include bilateral hilar adenitis and a low sensitivity to tuberculin. Also erythema nodosum is often seen in l.b. (Boström, 1940; Gravesen, 1942; Ask-Upmark, 1944; Löfgren, 1946; Ardell, 1946). Another point of similarity is that in l.b. joint pains sometimes occur (Löfgren, 1946; Ustvedt, 1949) and so does fever, especially in uveoparotitis.

It seems that Ustvedt is the first to have given any detailed consideration to the relationship between the BHL syndrome and l.b. In a work dealing with the nosography and diagnosis of l.b. 1939 he gave it as his opinion that the hilar lymphadenitis is almost always bilateral in l.b. whereas that associated with the primary complex of tuberculosis is usually unilateral. He therefore took the view that in cases where there was bilateral hilar adenitis one should always bear l.b. in mind as a possible diagnosis, not only when the tuberculin reaction was negative, but also when it was clearly positive. He also pointed out that l.b. often runs its course with only enlargement of the hilar nodes.

Ustvedt further developed his views on the connection between l.b. and the BHL syndrome in another work published in the same year (1939). In this he gave an account of 40 patients with bilateral hilar enlargement. 32 were tuberculin negative. Among the 40 cases there were 13 which could, with some degree of certainty, be described as cases of l.b., and an equal number in which the nature of the lesion was not clear. As to these latter, the enlargement of the hilar nodes disappeared during the course of observation over 1–3 years without any other symptoms having arisen which might have given a clue to the nature of the disease. In two of the cases there was pain, swelling and

stiffness of the joints at the onset. As to the etiology, Ustvedt says: "So far as I can see one cannot completely exclude the possibility that we are dealing with isolated, initial, and to some extent transient manifestations of Boeck's sarcoid. But, of course, it may be merely ordinary tuberculosis."

In his monograph on l.b. Gravesen (1942) described a couple of cases in which the triad erythema nodosum, bilateral hilar adenitis and negative tuberculin reaction was present. One of the patients also had joint pains. There were no definite facts to justify the diagnosis of l.b. but Gravesen put forward the possibility that some cases with these symptoms may be cases of l.b.

Abramson (1943) described four cases of erythema nodosum with bilateral hilar adenitis, tuberculin anergy, joint pains and fever of longer or shorter duration. There was no progress in the hilar lesions during a period of observation of 5–7 months, nor did any new changes appear in the parenchyma of the lungs during this time. Abramson was nearly convinced that his patients had l.b., although no other manifestations characteristic of this condition were seen. In an appendix to the work, however, he described how one of the patients, who gave no reaction with 5 mg tuberculin, developed unilateral pulmonary lesions, at which time the tuberculin reaction became positive. It was later discovered that the patient's husband was suffering from florid tuberculosis of the lungs.

In his monograph on erythema nodosum Skiöld (1945) gave an account of 35 cases in which this symptom was associated with bilateral enlargement of the hilar lymph nodes. 15 of these patients had been tuberculin tested and their sensitivity to tuberculin was compared with that of 39 other patients with unilateral enlargement of the hilar lymph nodes. It was found that those in whom the enlargement of the hilar nodes was bilateral had a considerably lower sensitivity to tuberculin than those in which it was unilateral. While the later course of the disease showed that 29 of the patients in whom the hilar enlargement was unilateral developed signs of tuberculosis, this disease did not appear in a single one of the patients in whom it was bilateral. As regards the etiology of the BHL syndrome Skiöld stated: "It was not possible to establish the disease origin in any of these cases of bilateral hilar processes. The roentgen picture of the lungs is strongly indicative of lymphogranulomatosis benigna (Schaumann). But there were no other symptoms pointing to this disease in these cases. On the other hand, the clinical picture of lymphogranulomatosis benigna is sometimes meagre, and so this fact does not gainsay the diagnosis. ... Certain facts, however, indicate that this condition (l.b.) was not present, at least in a number of the cases. Instead, it seemed that the cases were independent of lymphogranulomatosis benigna."

In his excellent work on the etiology and pathogenesis of erythema

nodosum Löfgren (1946) discussed the question of the etiology of the BHL syndrome. His main series comprised 178 cases of erythema nodosum in adults. In 30 (16.9 per cent) of these there was bilateral enlargement of the hilar lymph nodes and, in most cases, weakly positive or negative tuberculin reaction. 20 of them also showed changes in the parenchyma. Tuberculosis was demonstrated in 7 patients and was thought to be probable in another two (30 per cent) of the group with bilateral enlargement of the hilar nodes. In the other 21 cases, with one exception, no etiological factor could be found for the erythema nodosum. There was no tuberculosis or streptococcal infection which are the factors which usually play an important part in the pathogenesis of erythema nodosum. In 6 of the 20 cases with changes in the parenchyma these were of the type seen in l.b. From the clinical point of view and, probably, also from the radiographic point of view, these cases had certain features in common. During the first 2–3 months the bilateral lymph node enlargement appeared to dominate the picture while the changes in the parenchyma were relatively insignificant. It was not until the lymphomas began to get smaller that the parenchymatous changes began to progress. They dominated the picture from the third to the sixth month and then subsided. As the diagnosis of l.b. was verified by biopsy in two of these cases, Löfgren considered it to be probable that the other four cases as well had a connection with l.b.

Among the group described above, in which there were bilateral hilar changes and a negative or weakly positive tuberculin reaction, Löfgren distinguished 9 cases characterised by large and comparatively symmetrical lymphomas which represented the BHL syndrome of unknown origin. In 5 of these there were unilateral changes in the parenchyma and in this they were unlike most of the previously described cases of this syndrome. Löfgren said that "the separation of this group from the others must be regarded as tentative and to a certain extent subjective, but for the present it would seem to be justified because of the hypothesis advanced that nodal fever cases with these roentgen appearances and a negative tuberculin reaction might have connection with lymphogranulomatosis benigna. As the tuberculin reaction in lymphogranulomatosis benigna need not necessarily be negative (to 1 mg Mantoux) but can be weakly positive as well, it would seem to be correct also to place nodal fever cases with a weak or moderate tuberculin reaction in the group in question. It should be pointed out, however, that it has not yet been proved that this group has a connection with lymphogranulomatosis benigna or even that it is etiologically uniform."

Ardell (1946) also gave an account of a series of cases of erythema nodosum comprising 157 cases of which 23 (14.6 per cent) were tuberculin negative, including 9 in which there were changes in the lungs. Most of these were bilateral enlargements of the hilar lymph nodes. According to Ardell two of these patients definitely, and two probably,

had l.b. In most of the rest of the cases it was considered that the enlargement was due to some non-specific infection, probably streptococcal. This was suggested by the occurrence of sore throat in several of the cases. In a couple of the patients the tuberculin reaction changed from negative to positive when the hilar nodes got smaller. This seemed to Ardell to indicate that the infection temporarily lowered the allergy to tuberculin.

In 1949 Törnell reported on 43 cases of the BHL syndrome and l.b. He stated that, clinically, there was a continuous transition between the two conditions but that, in the individual case of the BHL syndrome, it was often hard to demonstrate its l.b. nature, by biopsy for example, since the enlargement of the hilar nodes quite often vanished without any other symptoms characteristic of l.b. having appeared.

The question of the etiology of the BHL syndrome was taken up again by Ustvedt (1949). He now put forward the view that bilateral hilar adenitis, with or without erythema nodosum, is not uncommonly due to tuberculosis, especially in those cases where the tuberculin reaction is strong, but also in cases where it is weak or negative. As for l.b., Ustvedt now considered that it is far less important in the cause of the BHL syndrome than tuberculosis.

The problem of the relation between the BHL syndrome and tuberculosis and l.b. has recently also been the subject of a detailed discussion by Löfgren and Lundbäck (1952). Their series consisted of no less than 212 cases of the syndrome, the number of women being 161 and the number of men 51. 113 (107 women and 6 men) of the 212 had erythema nodosum. The syndrome was commonest in the age group 25–29 years but was also common in the age groups 30–34 and 35–39 years. On the other hand, it was rare at those ages at which primary tuberculosis reaches its peak. A particularly interesting observation is a correlation in time between the development of the BHL syndrome and pregnancy or lactation.

The tuberculin reaction was positive for Mantoux 0.01–1.0 mg in 112 of the 212 cases but in the other 100 it was negative for the latter dose. A comparison between the tuberculin positive and the tuberculin negative groups in relation to tuberculosis gave interesting results. There was no difference between them in respect of a family history of tuberculosis. On the other hand, the tuberculin positive group contained 11 patients who had previously had manifest tuberculosis while the tuberculin negative group did not contain a single one. In the former group there were 22 and in the latter only 2 patients presenting calcified foci in addition to recent bilateral hilar lymphomas. Furthermore, in the tuberculin positive group signs of previous natural tuberculous infection could be domonstrated in 63.4 per cent of the cases while in the tuberculin negative group they were only present in 9.0 per cent. Tuberculosis only developed in one case in the whole series during a relatively long

period of observation. Guinea pig tests using gastric lavage fluid were carried out in 146 cases in all of which the results were negative. In 55 cases peripheral lymph nodes were taken for biopsy and in 43 of these the changes typical of l.b. were seen. Some of the lesions of the skin and mucous membranes also showed the same changes. On the basis of these observations Löfgren and Lundbäck formulated a theory concerning the etiology of the BHL syndrome. As it differs in several important respects from the classical primary tuberculosis they came to the conclusion that it is essentially independent, from the point of view of etiology, of tuberculosis and interpreted it instead as the primary stage of pulmonary l.b. This, therefore, is not, in their opinion, a tuberculous condition.

As has been shown above, the investigations of the past few years concerning the BHL syndrome have given extraordinarily interesting results. Its nosological relation to l.b. has been clarified and it has been shown that at least the majority of cases of the syndrome represent an early manifestation of l.b. The studies of the BHL syndrome have also led to a change in our views concerning the incidence and course of l.b. As Löfgren has recently (1953) stated, there is much to suggest that the disease is far commoner than has hitherto been supposed, and his work has shown that it often resolves within a couple of years. On the other hand, the studies on the BHL syndrome have scarcely contributed at all to our understanding of its etiology or of that of l.b. Good grounds have certainly been given for believing that the BHL syndrome is not a manifestation of the *classical* primary tuberculous infection. But this, of course, does not answer the question what part *atypical* primary tuberculous infection may play in determining its occurrence.

CHAPTER 4

Histopathology

As has already been pointed out, Boeck (1905) considered that the multiple benign sarcoid can be recognised by its very characteristic microscopic picture. According to him the distinguishing features of the disease is the occurrence of foci which are sharply demarcated from the surrounding tissue. These foci are formed of epithelioid cells with some admixture of giant cells but without caseous necrosis. Further points which he considered characteristic were the perivascular localisation of the granulomata, the complete destruction of elastic substance of the skin affected and the absence of perifocal lymphocytic reaction.

In his work *Recherches sur le lupus pernio et ses relations avec les sarcoïdes cutanées et sous-cutanées*, Schaumann (1917) described the microscopic picture as seen in the lymph nodes as follows: "L'étude microscopique relève, dans tous les ganglions examinés, un tissu néoformé absolument analogue à celui des lésions cutanées. Ce tissu, envahissant les ganglions en partie ou en totalité de manière à effacer plus ou moins l'architecture normale, est composé de follicules nettement limités, isolés ou confluents, dans la constitution desquels entrent des cellules épithélioïdes et des cellules géantes et qui sont encadrés par des cellules lymphoïdes et plasmatiques, groupées sur quelques points en masses compactes."

Schaumann said that he could not find caseous necrosis in the granulomata but "en quelques points la colorabilité des noyaux est diminuée au voisinage du centre des agglomérations épithélioïdes". He also considered it characteristic of the process that the granulomata are permeated by a delicate stroma of connective tissue which becomes coarser as the foci get older and leads to their sclerosis. In some of the giant cells he found peculiar, lamellated bodies. He was inclined to interpret them as degenerate hyphi of streptothrix, a fungus which he had succeeded in isolating from the affected lymph nodes. He did not, however, consider that this microfungus played any etiological part.

Schaumann's view as to the microscopical picture of l.b. has been accepted by most later authors as quite correct. It is also reflected by the definition given to l.b. by the Conference of Sarcoid, National Research Council, U.S.A. in 1948: "Sarcoidosis is a disease of unknown etiology.

Pathologically it is characterized by the presence in any organ or tissue of epithelioid tubercles with inconspicuous or no necrosis and by the frequent presence of refractile of apparently calcified bodies in the giant cells of the tubercles. The characteristic lesions may be replaced by fibrosis, hyalinization or both."

Although the microscopical criteria for l.b. given by Schaumann are still valid, the absence of caseous necrosis is not now considered essential for diagnosis. When Lewandowsky (1921), Pinner (1938) and others demonstrated the presence of this change in l.b., even though only to an almost insignificant extent, it raised the question of differentiating the condition from tuberculosis, including those atypical forms of the disease which are also characterised by having only a slight tendency to caseous necrosis. This was particularly important to those who could not accept the hypothesis that l.b. is tuberculous in nature. In this situation they began to look for details in the microscopic picture of l.b. which might facilitate the differential diagnosis between it and tuberculosis. With the passage of time the classical microscopic picture of l.b. has been filled out with many morphological details which, although they are not generally recognised as being specific for the condition, are, when taken together with the characteristic pattern of l.b., considered useful in differentiating between it and tuberculosis. These morphological details concern almost every element in the tuberculoid foci, the epithelioid cells, the giant cells, the stroma, and the vessels.

The Epithelioid Cells

Quite soon after Boeck had described the multiple benign sarcoid various authors stated that a certain number of the epithelioid cells in the cases which they had seen differed morphologically from those which are usually seen in classical tuberculosis. Thus Kyrle (1910) wrote of the epithelioid cells in a case of lupus pernio: "Die Herde selbst bauen sich zum grössten Teile aus epitheloiden Zellen auf. Und zwar sieht man neben solchen mit ziemlich gut färbbarem Protoplasma und Kern, Elemente, die vakuolenartig aufgebläht zu sein scheinen; es besteht ihr ganzer Zelleib aus einem hellen, fast nicht färbbaren Protoplasma, der Kern ist ganz an die Peripherie der Zelle gedrängt und umgibt oft halbmondförmig den Plasmaleib." Kyrle does not seem to have known what is the cause of the "large-celledness". He did not, either, suggest to what extent this cellular peculiarity was specific for lupus pernio. It is of interest that this atypical morphology of the epithelioid cells observed by him formed part of the basis of two disease names already mentioned, namely Ziegler's (1890) "Grosszellige Hyperplasie" and Mylius and Schürmann's (1929) "Universelle, sklerosierende, tuberkulöse, grosszellige Hyperplasie, eine besondere Form atypischer Tuberkulose".

The paper of Herxheimer and Roth (1916) entitled "Zur feineren Struktur und Genese der Epitheloidzellen und Riesenzellen des Tuberkels" gives a good account of the morphological basis and meaning of the obscure term large-celled hyperplasia. This paper was based on the study of 12 cases of what the authors believed to be tuberculous lymph nodes. In these studies Herxheimer and Roth used Benda's staining method for bringing out the finer details of cellular structure, preferably staining with iron alizarin and toluidine blue, as well as Heidenhain's iron hematoxylin staining method. Some years earlier Wakabayashi (1911) had observed centrosomes and centrospheres (microcentrum) in tuberculous giant cells and Herxheimer and Roth were able to demonstrate that these structures were also present in the epithelioid cells. In the middle of these cells they saw two or more structures made up of granules and sometimes hanging together by threads, which were clearly the same as the central bodies or centrosomes found by Wakabayashi in tuberculous giant cells. These were surrounded by an almost achromatic sphere, the centrosphere, which was sharply demarcated from the rest of the protoplasm and showed a delicate radial formation. Those epithelioid cells which contained a large centrosphere were completely dominated by it. They were rounded and their nuclei were often situated peripherally, bean-shaped and lay with their concave surfaces in direct contact with part of the surface of the centrosphere. In two of their cases which showed neither macroscopic nor microscopic signs of caseous necrosis a great number of the epithelioid cells had very large centrospheres. Herxheimer and Roth were very cautious in discussing the causes of the enlargement of the microcentrum but they stated that it might indicate that the cells in question were beginning to undergo amitotic division.

Herxheimer and Roth's observations, confirmed by later workers (Castrén, 1923, among others), illuminate the description of the morphology of the epithelioid cells given by Kyrle. There can be no doubt that when he wrote of atypical epithelioid cells he meant just such cells with hypertrophy of the centrosphere, a structure which must not have been known to him at the time when he made his communication.

Kyrle's work is of particular interest in that it probably contains the first reference, in connection with l.b., to a morphological detail which still later writers have considered as being characteristic of this disease. Thus Hamperl (1940), in a paper called "Zur Histologie der Boeckschen Krankheit" writes: "Bei der histologischen Untersuchung zweier ausgeschnittener Lymphknoten konnte ich einen Befund erheben, der bisher kaum berücksichtigt wurde: eine auffällige Vergrösserung des Zentralapparates in den Epitheloid- und Riesenzellen." Hamperl's description of the atypical morphology of the epithelioid and giant cells corresponds exactly with that given by Kyrle. With reference to the enlargement of the central apparatus (microcentrum) and its relation to normal

conditions he writes: "Während normalerweise nur zwei Zentralkörper vorhanden sind, bilden hier mehrere das kleine, zentrale Häufchen; die Sphäre, die sonst kaum in Erscheinung tritt, erreicht hier eine Grösse bis zu 10 μ ... Der Unterschied gegenüber dem normalen Verhalten besteht dabei mehr in einer quantitativen als in einer qualitativen Veränderung." He further maintains that the enlargement of the central apparatus "an und für sich nichts Kennzeichnendes für die Boecksche Krankheit darstellt. In darauf gerichteten Untersuchungen habe ich aber in gewöhnlichem tuberkulösen Granulationsgewebe ihn nur dort gefunden, wo die Epitheloidzellen zu grossen saftigen Elementen entwickelt waren, also nicht an der unmittelbaren Grenze zu einem Käseherd, sondern in einiger Entfernung von ihm, sozusagen an Stellen abgeschwächter Giftwirkung. Während man aber hier nach Zellen mit solchen vergrösserten Sphären suchen muss, waren sie in so gut wie allen Epitheloidzellen der beiden untersuchten Lymphknoten vorhanden und auf den ersten Blick zu sehen. Den gleichen Befund konnte ich auch in Fällen von Boeckscher Erkrankung der Haut erheben". Hamperl also considered the immediate cause of the enlargement of the central apparatus in l.b. and adopted the view put forward by Lewis (1920) that it is due to cell damage. He was thus inclined to interpret the enlargement of the microcentrum as a degenerative change which appears not only in l.b. but also in other conditions. He maintained, however, that the uniform and marked presence of this change in almost all the epithelioid cells supports the histological diagnosis of l.b.

Other authors than those just mentioned also take the view that there is a difference between the epithelioid cells in l.b. and those in tuberculosis. For example Rakov and Taylor (1942), in discussing the differential diagnosis between these two conditions, state: "Each attempt thus far to point out the distinguishing features between the sarcoid and the noncaseating tubercle has failed to convey in words what may readily be seen in sections. ... It seems to us that the epithelioid cells in the individual sarcoids are usually larger and more cubical ..."

What has been said shows that a single morphological detail has been considered by various authors as characteristic of l.b. The literature does not, however, make it clear whether the enlargement of the microcentrum occurs regularly in l.b.

The Giant Cells

All workers seem to be agreed that giant cells form an integral part of the microscopic picture of l.b. On the other hand, opinions are divided as to their frequency and morphology.

As far as the *frequency* is concerned Quinquaud, who, as has been mentioned, did the microscopic examination in the case of lupus pernio

described by Tenneson (1892), states that he found "la prédominance excessive des cellules épithélioïdes et une très grande rareté des cellules géantes". The view that the giant cells are less common in l.b. than in classical tuberculosis has also been shared by most of the more recent writers. For example, Pautrier (1940), in his monograph on l.b., writes: "Les cellules géantes sont rares; très souvent elles font totalement défaut. Parfois on en retrouve deux ou trois, ébauchées au sein des nappes épithélioïdes. Plus rarement on trouve soit de vraies cellules géantes isolées, soit même un groupement de deux ou trois cellules géantes, avec une couronne de noyaux complète." Blegvad (1931), Rist, Blanchy and Tuchila (1937), van Beek and Haex (1943), Teilum (1949) and others also emphasise the sparsity of the giant cells. Blegvad even goes so far as to cast doubt on the correctness of the diagnosis in certain reported cases of l.b. because there were numerous giant cells.

There are, however, exceptions to the rule that giant cells are uncommon in l.b. For example, in a case described by Seefelder (1937), in which there cannot be the slightest doubt as to the correctness of the diagnosis, there was a plentiful formation of giant cells, and the same was true of a case published by Lemming (1940) and examined microscopically by Lindau.

The question of the *morphology* of the giant cells has also been the subject of controversy as has already been mentioned. It was pointed out that Boeck (1899) described the giant cells in benign sarcoid as sarcomatous and considered that the presence of a large number of nuclei evenly distributed through the cytoplasm is characteristic of them. When he changed his opinion as to the etiological nature of the disease and called it benign miliary lupoid, he altered the name of the giant cells to Langhans cells. In his work of 1917 Schaumann simply used the term giant cells, but his illustrations show that these had the same morphology as those described by Langhans (1868) in his classical paper entitled "Über Riesenzellen mit wandständigen Kernen in Tuberkeln und die fibröse Form des Tuberkels". Several later authors (e.g. Rakov and Taylor, 1942; Thomas, 1943) also describe the giant cells as typical or true Langhans giant cells, by which they mean that there are relatively few nuclei which are situated peripherally and are usually collected at the poles of the cells. On the other hand, some authors describe them as atypical in comparison with the classical giant cells of Langhans. Thus Nickerson (1937) states that the giant cells in l.b. differ from those in classical tuberculosis in that they are usually larger and have more nuclei, often as many as 25–30, scattered over the whole of the plane of section. They thus lack the "elliptical" arrangement of the nuclei which he considers to be typical of the true Langhans giant cell. Bates and Walsh (1948) also mention the presence of atypical giant cells in l.b.: "The giant cells associated with sarcoidosis are usually larger and more irregular in shape than those seen i tuberculosis, frequently

have more nuclei (up to 30) and often show inclusion bodies of various sizes and shapes." Boyd (1944) and Lindau (in the case of Lemming, 1940) and others hold similar views. Thus Lindau expresses the opinion: "There are numerous giant cells, often of Langhans' type, but not seldom they appear more like foreign body giant cells."

On the other hand one may find in the literature views on the morphology of the giant cells which are diametrically opposed to those just discussed. Kissmeyer (1932), Rist, Blanchy and Tuchila (1937) and others express the opinion that the giant cells in l.b. are smaller and look shrunken in comparison with classical Langhans giant cells.

In studying the literature with a view to building up for oneself an idea of the frequency and morphology of the giant cells in l.b. one gets the impression that the differences in opinion are due to the fact that the authors concerned have made too many generalisations from too few observations. It is well known that the giant cells in classical tuberculosis show a high variability as concerns both frequency and morphology. This was already shown by Langhans (1868) and was also mentioned by Wakabayashi (1911): "Die Zahl der Kerne in den tuberkulösen Riesenzellen ist grossen Schwankungen unterworfen. Ebenso wechselt ihre Form."

The Inclusion Bodies

Many authors have remarked on the presence in l.b., as in some other granulomatous conditions, of bodies having a peculiar structure lying inside the giant cells. In principle these so-called inclusion bodies are of two types, first, the asteroid body, Wolbach's body (Skavlem and Ritterhoff, 1946), the spiculated body (Mallory, 1925) or the starfish body (Kay, 1950) and second, the more or less regular concentrically laminated body, the Schaumann body (Ricker and Clark, 1949, and others).

The asteroid body

Asteroid inclusions in giant cells of Langhans' type seem to have been first described by Wolbach (1911) in a paper entitled "A new type of cell inclusion, not parasitic, associated with disseminated granulomatous lesions". The material in which they were found was derived from five autopsy cases out of a series of 900. All of the cases showed widely distributed miliary sized granulomatous lesions, which were described as follows: "The lesions have considerable resemblance to miliary tubercles. They consist at first of groups of epithelioid cells and giant cells. Extensive necrosis or caseation does not occur. Complete cicatrization is the rule." As to the relation of the lesions to tuberculosis, which seemed to him the most likely disease to cause difficulty in differential diagnosis,

Wolbach wrote: "The absence of characteristic tuberculous processes in the body, the failure to find tubercle bacilli and the evolution of the lesions under consideration, exclude beyond reasonable doubt the possibility of tuberculosis in these cases."

A closer study of the cases reported by Wolbach shows that in the first the granulomata were localised to the lungs, in the second to the bronchial lymph nodes, and in the third to the lungs and their regional lymph nodes. In all these cases there was marked fibrous induration of the granulomata. In the fourth case there were lesions in the spleen, liver and lymph nodes, while in the fifth they were in the lungs, liver and spleen. Wolbach believed that neither the granulomatous process nor the inclusion bodies had ever been described before. The localisation of the lesions and the microscopic picture makes it seem probable that the cases described are ones of l.b.

As regards the nature and pathogenesis of the asteroids Wolbach expressed the view that they were composed of fibrin which had been phagocytosed by the giant cells and had then crystallised.

Iwanzoff (1912) reported that he had found giant cells with the same sort of inclusion bodies as those described by Wolbach in some small granulomatous foci in the uterus of a case of adenomyomatosis. He was very doubtful as to the etiological nature of the granulomatous process but considered that it might possibly be tuberculous. As to the nature of the asteroids he discussed the possibility that they represented degenerate centrospheres. He based this view on the morphological similarity between these inclusions and the centrospheres in tuberculous giant cells which had been described by Wakabayashi about a year before.

In 1913 Hummel described crystalline, star-shaped bodies in a granuloma with giant cells taken from a woman who may have been suffering from l.b. He considered that the asteroid bodies were formed by the crystallisation of some substance within the cell.

In 1914 Kranzfeld described granulomatous lesions in the spleen of a man who had died of generalised peritonitis. The granulomata were markedly indurated and contained numerous giant cells, each with a large number of nuclei which were usually distributed throughout the protoplasm. In vacuolated areas in some of the cells he found star-shaped formations, which, judging from his description, are the same as Wolbach's asteroids. Kranzfeld was cautions in discussing the etiology of the granulomatous process. After advancing arguments as to why it could not be luetic, actinomycotic or tuberculous he writes: "Aber dennoch legt das histologische Aussehen immer wieder den Gedanken nahe, dass doch Tuberkulose vorliegt; dafür spricht die Bildung der submiliaren, gefässlosen Knötchen, ihre Zusammensetzung aus epitheloiden Zellen, das reichliche Auftreten von Riesenzellen." A careful study of the work of Kranzfeld shows that the granulomatous process is probably

l.b. This supposition is supported, not only by the microscopical picture, but also by the fact that he was unable to find acid-fast rods in the granulomata. Like Iwanzoff he was inclined to regard the inclusions as pathologically changed centrospheres.

In his textbook *The principles of pathologic histology* Mallory (1925) figures a giant cell containing spiculated spherical bodies. Of these bodies he says that they "have been found in the spleen in a few instances inclosed in endothelial leukocytes and giant-cells. They may be quite numerous and occur in foci or diffusely scattered. The lesion resembles miliary tuberculosis, but no necrosis is produced. The bodies seem chemically to be of a fibrinoid character. They are evidently not the cause of the lesion, which is probably of infectious origin, but a secondary formation". The disease which Mallory is here describing is probably l.b.

In 1935 Orsos published the results of his studies of the pathology of the centroplasm (microcentrum) in tuberculosis and other conditions. According to him, the commonest change in the centroplasm of the epithelioid cells is hypertrophy, with the result that the greater part of the cell body is taken up by the centroplasm and the nucleus is displaced to the periphery. In such cases the tubercles appeared "siebartig durchbrochen, die hellen Lücken entsprachen den ungewöhnlich grossen zartgebauten Zentroplasmen". He also found marked hypertrophy of the centroplasm in the Langhans giant cells. The most striking phenomenon was that seen in lymph nodes with numerous tubercles. In most of the giant cells there were asteroid bodies, which he interpreted as being hypertrophic centrospheres. In regard to both morphology and staining properties the asteroids are similar to those described by previous authors. The substance from which the centrospheres are made he called linin, the condition in which they are pathologically enlarged and the amount of linin is increased he called hyperlinosis.

In the hypertrophic centrospheres of the giant cells Orsos often found degenerative changes in the form of liquefaction and calcification of the rays. The liquefaction sometimes proceeded so far that the increased linin of the hypertrophic centrospheres was completely liquefied. In such cases they were represented either by a single large vacuole or a system of smaller ones. In some cases the remains of the linin became calcified, sometimes before liquefaction set in and, in such cases, the calcification could proceed throughout the rest of the cytoplasm and result in more or less complete calcification of the giant cells. The illustrations to Orsos' work show that the formations which he believes to arise in this way are the same as the so-called Schaumann bodies. The particular interest in his work lies in the fact that in it the asteroids and the Schaumann bodies are, for the first time, considered together from a pathogenetical point of view. It is not possible to tell whether Orsos' cases are ones of l.b. as the description is very scanty.

As the earlier discussion has shown, the presence of asteroid bodies has

been noted especially in cases in which the localisation and the microscopic picture of the lesions gives rise to the suspicion that the condition is what, using the present day nomenclature, we should call l.b. As this disease has become better known the asteroid bodies have become more closely associated with it. In the work on the histology of l.b. to which reference has already been made, Hamperl (1940) noted the presence of asteroid bodies in the disease. He considered that they represent protein crystals which have arisen as a result of the disintegration of the enlarged centrospheres. In his textbook of pathology (1950) he expressed the same view and, like Orsos, stated that the asteroids sometimes become calcified and thus give rise to Schaumann bodies. Further, Lever and Freiman (1948) found asteroid bodies in 10 per cent of 70 cases of l.b. and Ricker and Clark in 2 per cent of 300 cases of the same disease. Among authors who have noted the presence of asteroid bodies in single or relatively few cases of l.b. may be mentioned Jadassohn (1919), Nickerson (1937), Voldet (1941), de Montmollin (1943), Friedman (1944), Skavlem and Ritterhoff (1946), Kay (1950) and Longcope and Freiman (1952).

Opinions vary as to the specificity of the asteroids for l.b. and their differential diagnostic significance. Some workers (e.g. Voldet) consider them to be specific for the disease and therefore assign great differential diagnostic significance to their presence in the individual case. This would, however, seem to be wrong. The literature gives clear evidence that asteroids may occur in various *local* granulomatous processes in the absence of l.b., for example in lipid or talc granulomata (Engle, 1953). It is, however, only in exceptional cases that these would be likely to be confused with l.b. It has already been shown, on the other hand, that the differential diagnosis between l.b. and certain forms of tuberculosis may present great difficulty. The question arises as to how far the asteroid bodies can be used in the differential diagnosis in this regard. Herxheimer and Roth maintain that they have observed asteroids in a case of tuberculosis. Other authors (e.g. Ricker and Clark, 1949) also state that asteroid bodies are to be found in tuberculosis. There can, however, be little doubt that asteroid bodies are considerably commoner in l.b. than in classical tuberculosis. Friedman's (1944) remark that "the asteroid may be non-specific but is highly characteristic of l.b." seems to reflect the views of most workers.

The Schaumann body

The first description of the concentrically laminated body later called the Schaumann body is to be found in Schüppel's (1871) work *Untersuchungen über Lymphdrüsen-Tuberkulose*. He there reported on 40 lymphomata which he believed to be tuberculous and which he had studied carefully, and followed this up with a discussion of the patho-

logical anatomy and histogenesis of tuberculosis of the lymph nodes. Case 1 of his series is of especial interest in this connection. He describes it as "Primäre Tuberkulose der hyperplastischen Halsdrüsen (Körniges Lymphom)". This was a young man who had previously suffered from ophthalmia, erythematous and eczematous eruptions on the lips and nose and enlargement of the lymph nodes. At the time of examination there was a number of nodes left, on the neck and in the parotid region. The cut surface of the excised lymph node was found macroscopically to be scattered all over with small translucent nodules. There was no caseous necrosis. Microscopically the node was found to be studded with a large number of tubercles of fairly uniform size. The giant cells had a remarkably large number of nuclei and in them Schüppel observed concentrically laminated calcified formations, clearly Schaumann bodies. He considered them to be concrements which had arisen as a result of regressive changes in the cytoplasm of the giant cells. The clinical picture in this case is the feature which most clearly indicates that it is one of l.b.

In a work which deals primarily with the question of the phagocytic properties of the giant cells and, in particular, with their ability to phagocytose elastic fibres, Ssudakewitsch (1889) stated that he had found concentrically laminated inclusion bodies in the giant cells in a case of lupus vulgaris. To judge from his description of the microscopic character of the lesion there is a suspicion that, here too, we are dealing with a case of l.b. He writes: "Ich fand keine scharfen Erscheinungen einer regressiven Entartung: nur in seltenen Fällen erschienen in den compacten Infiltraten einzelne Zellengruppen etwas getrübt und mit Kernen, welche weniger energisch Farbstoffe aufnahmen. Ausserdem fanden sich auch hier hyaline Schollen ... Die einzelnen Knötchen erinnerten lebhaft an Tuberkeln, obwohl die Färbung auf Tuberkelbazillen zu einem negativen Resultate führte." Ssudakewitsch considered that the concentric bodies in the giant cells represented the remains of phagocytosed elastin.

In 1903 Gilchrist and Stokes reported that they had found calcified, concentrically laminated bodies in the numerous Langhans giant cells in a granuloma tissue which they described as lupus-like. The material examined consisted of skin and lymph nodes. They could not find any acid-fast rods in the sections, but a guinea pig, which was inoculated with lymph node tissue, died a month later, and post mortem examination showed miliary nodules in the liver. No acid-fast bacteria could be found in these either, but they contained bodies of the same type as were found in the human material. Inoculation into a dog gave a generalised adenitis with calcified bodies like those seen in the guinea pig. Gilchrist and Stokes thought they might be associated with parasites.

Askanazy (1921), under the title "Über lupöse Tuberkulose des Blutbildungsapparats und tuberkulöse Splenomegalie", described an autopsy

case which Kay considers to have been one of l.b. There were lesions in the skin of the face, the lungs and the abdominal lymph nodes as well as the bone marrow and spleen. The morbid process was found, microscopically, to consist of sharply limited, non-caseating miliary tubercles with a marked tendency to fibrous induration. In the lymph nodes Askanazy observed laminated calcified bodies. Attempts to demonstrate acid-fast bacteria in sections of the spleen failed, but some were found in smear preparations made from a suspension of splenic tissue in antiformin.

As the concept of l.b. has beçome better known the concentrically laminated bodies included in the giant cells have come to be associated with the disease. Even in his first work on l.b. Schaumann (1914), as already stated, described the occurrence of these bodies and in 1917 he gave a comprehensive description of them. He describes them as follows: "Ces corpuscules varient considérablement comme dimensions et configurations. Les plus petits que j'ai observés sont du volume d'un leucocyte et de forme arrondie ou ovalaire. A ce stade, ils sont approchés de l'un des pôles de la cellule géante, isolés ou deux ensemble et paraissent entourés d'une membrane dont les deux contours se colorent fortement au bleu polychrome, à la thionine phéniquée et à certaines autres couleurs, alors que le reste du corpuscule se fait remarquer par une réfringence plus ou moins notable. Au fur et à mesure que ces corpuscules augmentent de volume, ils s'approchent du centre des cellules géantes. En même temps la structure se modifie en tant que le double coutour de l'enveloppe paraît moins visible ou s'efface tout à fait et que la formation semble composée d'un certain nombre de lamelles concentriques ... C'est dans les ganglions lymphatiques et spécialement dans les amygdales — organes où abondent les foyers tuberculoïdes — que j'ai trouvé ces formations curieuses. En général, elles se rencontrent à l'intérieure de cellules géantes, qui diminuent de netteté et de colorabilité selon que les inclusions augmentent de volume." Schaumann thought that the bodies probably arose as the result of concretion of degenerate streptothrix fungi. He supported this view by the observation that similar formations may sometimes be seen in old cultures of streptothrix derived from organs affected with l.b. As he thought that the streptothrix fungi seen in l.b. were only saprohytes he did not consider that the inclusion bodies were specific for this disease.

In later works Schaumann also put forward his opinion as to the nature of the concentrically laminated formations. In 1941, he referred to an observation of Metchnikoff (1888) that inoculation of tubercle bacilli on the Algerian gerbil, which is particularly resistant to tuberculosis, causes characteristic lesions in which their are giant cells containing bodies of exactly the same type as those seen in l.b. Correlating his own observations with those of Metchnikoff, Schaumann maintained that "the micro-organism of tuberculosis is capable of entering into the genesis of

the corpuscles present in the tissue of tuberculous affections, including lymphogranulomatosis benigna".

Thus, the strongest evidence for Schaumann's opinion that the bodies were altered tubercle bacilli was the result of Metchnikoff's experiments and the ideas formed by him as to the pathogenesis of these bodies. It seems, however, hardly likely that the bodies observed by Metchnikoff, which are undoubtedly the same as the Schaumann bodies, are formed by altered tubercle bacilli. It would seem more likely, as Teilum (1949) also suggested that, by the injection of tubercle bacilli into the Algerian gerbil, Metchnikoff elicited a special tissue reaction caused by the strong resistance of this animal to tuberculosis, and that the concentrically laminated bodies in the giant cells formed a characteristic feature of this reaction. Such an interpretation would also explain why Schaumann bodies have also been found in lupus (Lang, 1875; Pelagatti, 1901), which, according to current views, occurs in people who have a relatively high resistance to tuberculosis.

It has already been mentioned that Tillgren (1935) described a case of l.b. with diabetes insipidus as the most prominent symptom. Wahlgren, who did the autopsy, found chromatophilic bodies with a concentric structure in the granulomata in the hypophysis, some of these were enclosed in the giant cells, while others lay free in the tissues. In 1937 Berg and Bergstrand described a case of l.b. with Schaumann bodies in the giant cells. They considered that these had arisen as a result of the phagocytosis of elastic fibres. In the same year Seefelder reported a case of l.b. with Schaumann bodies. He stated that his observation of such bodies in l.b. was new and maintained that they had only been found in tuberculosis previously, a statement which is obviously false.

In his review of the morbid anatomy of l.b. Wahlgren (1937) stated that he had often found Schaumann bodies in the lymph nodes and lungs. Likewise, Bates and Walsh (1948) stated in an account of 7 cases of l.b. that many of the giant cells contained inclusion bodies of "various types", among them Schaumann bodies. In a case of coexistant pulmonary asbestosis and l.b. Skavlem and Ritterhoff (1946) found inclusions of the Schaumann variety in about 4 per cent of the giant cells. They affirmed that these formations are often doubly refractive, a feature which they did not think had been noted previously. They also found asteroid bodies in about 1 per cent of the giant cells. So far as they knew simultaneous occurrence of both types of inclusion body had not been described previously. It has, however, been mentioned already that the German authors (Orsos, 1935; Hamperl, 1940) had not only noted the simultaneous presence of asteroids and Schaumann bodies in l.b. (and ordinary tuberculosis?) but had even expressed the view that there is a pathogenetic relationship between the two types of inclusion.

At the Eighth Scandinavian Pathological Congress in Uppsala in 1947 Refvem gave a lecture entitled "'Boeck's disease' and occurrence of

minute mineral particles" in which he put forward the possibility that these crystalline formations, which the illustrations showed to be Schaumann bodies, were exogenous and had entered the body by the inhalation of dust containing minerals. He supported this view by the fact that some authors have found that people living in the country are preferentially attacked by l.b., and also by fact that the soil in cambro-siluric regions contains particles of calcareous spar with diameters of only a few microns. According to Refvem, such particles might be lifted by the wind and inhaled and then settle in the lungs or in other places and cause localised forms of l.b. It seems possible, according to him, that such particles might give rise to more generalised disease by means of lymphatic and hematogenous spread. It seemed to him that the absence of mineral particles in the granulomata in some cases of l.b. might be only apparent and be due to the fact that they are so few in such cases that they escape detection on microscopic examination, or their absence might be due to the solution of the crystals during the development of the granulomata. Thus he believes that some cases of l.b. represent a more or less generalised foreign body reaction. Finally he stated: "It is possible that the so-called atypical and slightly virulent species of tubercle bacilli, which are proposed to be responsible for some cases of Boeck's disease, and which cannot be cultivated, actually are not bacteria, but are related to minerals." One gap in Refvem's study seems to be that he did not discuss the question whether the Schaumann bodies can be formed within the granulomata. If they can, their presence in l.b. ought properly to be regarded as the result rather than the cause of the disease.

Teilum (1948) expressed the opinion that the morphologic lesions in l.b. represent a serologic hyaline (paramyloid) precipitation with an allergic hyperglobulinosis in the reticulo-endothelial system as the underlying primary cause. He based this partly on the fact that plasma cells are sometimes present in large numbers in the affected organs and partly on the fact that hyperglobulinemia has been demonstrated in many cases (Salvesen, 1935; Fisher, 1939; Harrell, 1940; Bing, 1940; Fisher and Davis, 1942). In accordance with this view Teilum (1949) stated that the stratified bodies in l.b. are due to biochemical, partly crystalline precipitates of the nature of a globulin in the cytoplasm of the giant cells, where the bodies mentioned behave like foreign bodies. He supports this view by the fact that when Schaumann bodies are stained by Unna's method they take a red colour which indicates that they contain ribose nucleotide. Furthermore, both with this method and with that of Masson he was able in several areas corresponding to the presumably earlier stages of precipitation to demonstrate intensely red-staining crystalline precipitates, or confluent hyaline droplets which also stained red, in direct relation to the protoplasm of the reticulum cells. It was his opinion that the intracellular precipitates gradually became encrusted

with iron and calcium. Teilum's statement that the asteroid bodies doubtless must be considered as being of the same nature as the Schaumann bodies is of particular interest; it is a view which was, as has already been stated, also held by Orsos and Hamperl.

In his monograph on l.b. to which reference has already been made, Vogt (1950) gave an account of nine autopsies which he had performed himself. In three of these, Schaumann bodies were found in various organs. He states that, after decalcification and staining for elastin, spirally twisted homogeneous threads which sometimes took a dark blue colour appeared in the concrements. He therefore considered that they represented degenerated and calcified elastic fibres.

Among other authors who have noted the occurrence of Schaumann bodies in a few or in single cases of l.b. the following may be named: Mylius and Schürmann (1929), Lindau (1938 and 1940, in the latter year in the case of Lemming), Lindau and Löwegren (1940), Leitner (1942), Kraus (1942), Rubin and Pinner (1944), Hogan (1946), Scotti and McKeown (1948), Ricker and Clark (1949), and Jaques (1952). The last-mentioned author called attention to the resemblance of the lamellae of the Schaumann bodies to chitinous material and postulated that a nematode infestation may be responsible for some cases of l.b.

As has been shown, there are remarkably varied opinions as to the nature of the Schaumann bodies. The same may also be said of their differential diagnostic significance. The disease which it is often hard to distinguish from l.b. both clinically and histologically is tuberculosis in certain of its forms. The question of the differential diagnostic significance of the Schaumann bodies depends therefore on whether the bodies occur in this disease as well. Opinions are divided on this point. Broadly speaking one can distinguish two views. The first is put forward by Rich (1951) in his well-known work *The pathogenesis of tuberculosis*, where he uses the following as one of his arguments against the view that l.b. is a tuberculous disease: "The giant cells in sarcoid lesions commonly contain characteristic, often concentrically laminated, refractile of calcified bodies, which are never encountered in unequivocally tuberculous lesions in man or the ordinary laboratory animals." According to the other view, put forward by Schaumann (1941), among others, the bodies are not specific for l.b. but may be seen in other conditions e.g. lupus vulgaris. However, some authors (Berg and Bergstrand for example), while they do not go deeply into the question of whether the Schaumann bodies are specific to l.b., consider that their presence, in association with other morphologic lesions characteristic of l.b., is of value in distinguishing between this disease and tuberculosis. The same opinion is expressed in the declaration of the Conference of Sarcoid, National Research Council, U.S.A., in 1948 (see p. 33).

Regressive Changes

Caseous Necrosis

As has already been mentioned, there was no caseous necrosis in the three cases of l.b. which Schaumann described in 1914. He did, however, as already stated, very occasionally find a diminished colorability of the epithelioid cells in the central parts of the tuberculoid foci. This was present in the granulomata in the skin as well as those of the lymph nodes and tonsils. Such diminished colorability of the epithelioid cells, which would naturally be regarded as an indicative of necrobiosis, has also been observed by later workers. Some of these also speak of a more pronounced cellular necrosis occurring at the centres of the granulomata, but they consider that this should be regarded as quite distinct from caseation. For example Boyd (1944) writes on l.b.: "There is a striking and characteristic absence of caseation although the central cells may be necrotic."

The question as to whether caseous necrosis does ever really occur in l.b., and whether the presence of such necrosis can be considered compatible with such a diagnosis has been the subject of eager discussion. While some authors, like Boyd, express the opinion that true caseous necrosis never occurs in l.b. or even, like Nickerson (1937) for example, regard the absence of caseation as a diagnostic criterion, there are others who consider that caseous necrosis is sometimes seen, though in insignificant amounts, and that the presence of this change is therefore perfectly compatible with such a diagnosis. The latter group of authors, among whom Pinner (1938), Rubin and Pinner (1944) and Vogt (1950) may be included, support their view by personal observation of caseous necrosis in undoubted cases of l.b. In a collection of 26 cases of l.b. in which an autopsy had been performed, derived from the literature, Rubin and Pinner stated that some caseous or necrotic foci had been observed in eight. They maintain that "the more autopsy reports are published, the more it is realized that some caseation not infrequently occurs and that it cannot be accepted as a criterion against the diagnosis of sarcoidosis".

If these observations are correct and another degenerative change occurring in l.b., namely the so-called fibrinoid degeneration (see below), has not been misinterpreted as caseation, the question as to whether caseous necrosis occurs and is compatible with a diagnosis of l.b. must be answered in the affirmative.

Fibrinoid Necrosis

In his paper on lupous tuberculosis of the hematopoietic apparatus and tuberculous splenomegaly to which reference has already been made, Askanazy (1921) writes as follows: "In van Gieson-Präparaten ist das

fasrige Gewebe der Cutis im Bereiche der Tuberkelknötchen oft nicht mehr rot, sondern gelb gefärbt, hat also fibrinoiden Charakter." It has already been pointed out that the case reported by Askanazy was probably one of l.b. (Kay, 1950).

Another description of fibrinoid degeneration in l.b. has been given by Pautrier (1940) in his monograph on l.b. He gives a figure of a granuloma and states that the dark thread-like structures which are to be seen in the picture in the centre of the granuloma represent fibrinoid degenerate fibrils.

Robb-Smith (1947) states that it is not infrequent in l.b. to find small areas of fibrinoid change in the centre of the tubercle. The meaning of his term, fibrinoid change, is not, however, clear as he does not give an account of the morphology or probable pathogenesis of the lesion. It may be that he uses this term to denote the same phenomenon which Lindau and Löwegren (1940) state that they saw in l.b., namely that "the central parts of the foci stain but faintly and show fibrinoid exudation".

The first detailed description of the fibrinoid necrosis in l.b. is given by Ricker and Clark (1949). In a series of 300 cases of the disease they found this type of necrosis in 35 per cent. According to them minute areas of such necrosis can be seen in the centres of individual granulomata but the greatest amount is to be found in the areas where several granulomata coalesce. The fibrinoid necrosis is strongly eosinophilic, fibrillar and acellular apart from a few intact lymphocytes which are to be found about the periphery of the necrotic area. This kind of necrosis is considered by Ricker and Clark to be characteristic of l.b. and they state that "it is in the total lack of cells and cellular debris with homogeneous, fibrillar zones of necrosis that this type is distinguished from the caseation of tuberculosis".

A regressive change in a granuloma in l.b. which is clearly of the same type as that described by Ricker and Clark is mentioned and figured in the Color Atlas of Pathology, prepared under the auspices of the U.S. Naval Medical School (1950). The centre of the tuberculoid focus there figured seems to be the site of caseous degeneration. However, the legend states that the area in question shows "a delicate reticulum, not to be confused with necrosis".

Kay (1950), in his work on l.b. of the spleen, writes that "central fibrinoid degeneration is often seen in sarcoid tubercles".

The literature does not state whether the change in the granulomata described by Ricker and Clark in l.b. also occurs in the Ziegler form of tuberculosis. It has, however, been shown by v. Albertini (1943), among others, that fibrinoid degeneration of collagenous connective tissue may occur in tissues affected by classical tuberculosis, especially the tendon sheaths, but in those cases it would seem that the degeneration only occurs outside the granulomata, especially in the area between tubercles which lie close to one another.

Perifocal Inflammatory Reaction

While the classical tubercle is surrounded by a band of lymphocytes of varying width there is, in l.b., either no, or at most an insignificant degree of perifocal inflammatory reaction. This was already mentioned by Boeck (1905) and it has also been noted by later workers as a characteristic of l.b. Thus Zieler (1914), for example, speaks of "naked" tubercles. The absence of inflammatory reaction surrounding the granulomata results in their sharp demarcation from the surrounding tissue. This fact is regarded by many authors as an important point in the differential diagnosis between classical tuberculosis and l.b. For example, as early as 1904 Kreibich wrote: "Das Charakteristische des histologischen Bildes liegt in der scharfen Umgrenzung der Herde. Während bei Lupus vulgaris die Grenze zwischen Tuberkel und Bindegewebe durch das periphere Rundzelleninfiltrat undeutlich wird, bilden beim Lupus pernio epitheloide Zellen und Rundzellen einen geschlossenen Herd welcher nicht selten von 1–2 Zügen konzentrisch angeordneter Bindegewebszellen umgeben ist." Zieler found the "naked" tubercles of l.b. so characteristic that he thought that they would enable him to make the diagnosis at first sight. Some authors (Pautrier, 1940, for example) consider that this insignificant amount of perifocal inflammatory reaction is a histological expression of the sluggishness which characterises l.b. clinically.

Even in his first work on l.b. Schaumann (1914) stated that he had found numerous plasma cells between the granulomata, especially in the tonsils and lymph nodes. A similar observation was also made by Teilum (1948) in a case of l.b. The presence of large numbers of plasma cells in tissues affected by l.b. is of great theoretical interest in view of modern theories as to the relation between this type of cell and the production of antibodies and hyperglobulinemia which quite often occurs in l.b. Teilum thinks, as has already been noted, that certain of the features of the microscopic picture of l.b. are expressions of an allergic hyperglobulinosis of the reticuloendothelial system, determined by persistent or repeated stimulation of immune mechanisms. The presence of large numbers of plasma cells in tissues affected by l.b. has, however, only been noted sporadically, and, as far as the present author can see, Teilum is the only worker who has put it in relation to the hyperglobulinemia and the morphology in this disease.

It has already been mentioned that eosinophilia, often quite considerable, is not infrequently seen in l.b. It might therefore be expected, by analogy with other conditions such as bronchial asthma, that there would be some degree of eosinophilia in the affected tissues, either in the granulomata themselves or in their neighbourhood. Lindau (1935) stated that he had been unable to find any information about tissue eosinophilia in l.b., nor had he seen it himself. However, in recent years a number of workers (van Beek and Haex, 1943; van Rijssel, 1947; An-

dersen, Christensen and Kjems, 1949; Baird, Bogoch and Fenwick, 1950) have noticed a varying number of eosinophilic leukocytes in the granulomata. According to van Beek and Haex the leukocytes in tubercles are mostly neutrophilic while those in the granulomata of l.b. are mostly eosinophilic. Van Rijssel has, however, pointed out that the presence of eosinophils in the granulomata is not specific for l.b. According to him eosinophilic leukocytes are to be found in both classical tuberculosis and l.b. and the younger the lesions the commoner are eosinophils.

Finally, it may be noted that Schaumann (1934) noticed the presence of large numbers of mast cells in tissues affected by l.b.

The reticulum. Indurative Changes

It has long been observed (Virchow, 1864) that, especially in productive tuberculosis, the tubercle is permeated by a fine reticulum. Certain modern American authors, however, deny that this is the case (Bates and Walsh, 1948). Nevertheless, using a silver impregnation method, the German worker Freesen (1950) has been able to demonstrate an argyrophil fibre network in the tubercle. In the chronic productive form of tuberculosis this reticulum becomes coarser. This process of induration leads to the formation of the so-called hard or fibrous tubercle (Virchow, 1864).

The granulomata of l.b. are also often referred to as hard tubercles (Thomas, 1943) and, as Rosenthal and Feigin (1948) among others have stated, the presence of reticulum fibres between the epithelioid cells of the granulomata is characteristic of the disease. This view is also shared by the majority of workers on the subject. Robb-Smith (1938), however, holds a different opinion. In a talk on the differential diagnosis between Wolbach-Stengel's sclerosis and l.b. he stated that in the latter disease the fibrils do not run between the epithelioid cells. His opinion on this point has, however, been criticised by Kay (1950), among others, who takes the view that the granulomata in l.b. are permeated by reticulum fibres.

A characteristic feature of the pattern of the stroma in l.b. is the tendency of the reticulum fibres as well as the epithelioid cells in the periphery of the granulomata to be concentrically arranged (Kreibich, 1904; Robb-Smith, 1938; Ricker and Clark, 1949; Kunkel and Yesner, 1950).

As the tuberculoid foci grow older there sets in a change which is characteristic of l.b. It consists in fibrohyaline induration which usually begins in the periphery of the granulomata. These gradually assume the character of more or less evenly rounded foci consisting of hyalinised, cell-poor, collagen connective tissue. As has already been mentioned, Teilum (1948) considered that the basis of the pathomorphology of l.b. is to be found in an allergic hyperglobulinosis of the reticuloendothelial

system determined by persistent or repeated stimulation of immune mechanisms. In accordance with this theory he would consider that the hyaline material represents in altered globulin precipitate.

The Blood Vessels

There are different opinions as to the occurrence of blood vessels in classical tubercles. Several authors consider that the lack of blood vessels in the tubercle is a characteristic feature of its structure. Thus, Herxheimer (1922) writes, in his textbook of pathology: "Kennzeichnend ist für die Tuberkel, dass sie die Blutgefässe entbehren, weil diese am Ort der Tuberkelbildung frühzeitig zugrunde gehen und die Neubildung selbst keine Gefässe enthält." Huebschmann (1928) formulates his opinion as follows: "Es ist eine alte Lehre, die immer wieder bestätigt wird, dass der eigentliche Epitheloidzellentuberkel gefässlos ist." Further, Lubarsch (1928) writes in Aschoff's textbook that the tubercle is characterised by its poor supply of blood vessels but that vessels are occasionally to be seen in its peripheral parts. However, on the basis of a thorough examination of tuberculous granuloma tissue, Putschar (1930) states that the old teaching that tubercles have no blood vessels is wrong. In some of his cases there were quite numerous capillary vessels. Some of these he considered to be newly formed.

As far as l.b. is concerned, there seems to be a fairly widespread opinion that the granulomata are quite often supplied with vessels. As has already been pointed out, the tuberculoid foci often develop round vessels which are usually not destroyed. This was pointed out by Boeck as early as 1899. Since his work the perivascular localisation of the epithelioid cell foci has only been discussed by a few authors, e.g. Kuznitzky and Bittorf (1915), Lewandowsky (1921) and Kissmeyer (1932). The last author writes: "Les infiltrations primitives gardent, dans leur développement suivant, leur caractère périvasculaire, suivant souvent les ramifications des capillaires." It seems clear that this description refers to the original vessels of the affected tissues. Kay (1950), among others, considers that the reason why the granulomata of l.b. do not necrose more than they do is the fact that they are so often provided with capillary blood vessels.

In his interesting work, to which reference has already been made in other connections, Teilum (1948) draws attention to a change occurring around the blood vessels in l.b., namely perivascular fibrosis. Thus, he found in both the affected spleen and lymph nodes in one case of the disease, a number of smaller vessels surrounded by broad rings of a hyaline substance which took an intense blue colour with Mallory's stain. Between these blue hyaline rings there were red lamellae. Peripheral to the perivascular hyaline there were often granulomata, surrounded

by hyaline bands displaying a direct continuity with the periarterial rings. This change resembles the periarterial fibrosis in the spleen in lupus erythematosus disseminatus. According to Teilum the ring-shaped perivascular hyalinosis is a morphological expression of the allergic hyperglobulinosis of the reticuloendothelial system which he believes to occur in l.b.

The vessels are occasionally the seat of inflammatory processes in l.b. Kuznitzky and Bittorf (1915) demonstrated granuloma tissue invading a vein, and Staehelin (1942) described periarteritis nodosa like lesions in various organs. Vascular lesions have also been reported by Urban (1910), Rosenthal (1949) and Wätjen (1952).

Microscopical Differential Diagnosis

Opinions differ widely as to the possibility of making a sure microscopical differentiation between l.b. and *tuberculosis*. Some authors maintain that it is a matter of the utmost simplicity while others consider that it often involves great difficulty.

Boeck is one of the leaders of the former school of thought. In his work of 1905 he stated, as already mentioned, that if a case presents diagnostic difficulties all doubt may be banished at once by a microscopical examination. One finds the same opinion as to the value of biopsy in the works of a number of the leading later workers. Thus, Gravesen (1942) maintained that the lymphadenitis of l.b. could usually be easily distinguished clinically from tuberculous adenitis, that in doubtful cases the tuberculin reaction might be helpful, but that biopsy was the only way of obtaining a certain diagnosis. Further, Bates and and Walsh (1948) stated: "Biopsy provides the only certain method of identification of sarcoid. The histological features of sarcoid are definite and usually unmistakable."

The aforegoing authors, however, do not seem to have been aware of the existence of atypical form of tuberculosis. Thus, as to the second view, namely that the microscopical differentiation between l.b. and tuberculosis may be fraught with great difficulty, it must be pointed out that this does not refer to the classical form of tuberculosis but to the forms of the disease which are often grouped together, especially by the German writers, under the term atypical tuberculosis. This group includes the large-celled hyperplasia described by Ziegler (1890) and referred to earlier. He describes it as follows: "Die ganze Erkrankung besteht alsdann wesentlich in einer fortschreitenden Neubildung von epitheloiden Zellen, welche kleine knötchenförmige Herde bilden ... Verkäsungsprocesse pflegen hierbei lange auszubleiben, doch kann sich das grosszellige Gewebe nach einiger Zeit da oder dort in eine gleichmässige hyaline oder aus glänzenden Schollen zusammengesetzte kernlose Masse

umwandeln." It follows from this description that the Ziegler form of tuberculosis resembles l.b. in many ways. The authors who, in spite of this similarity, consider l.b. to be a disease *per se*, must experience great difficulty in the microscopic differentiation between the two conditions. In many works, such as that of Cone (1948), there occur expressions such as "suggestive of" or "consistent with" l.b. in the pathological reports. The position of the pathologists in regard to a certain group of cases is, perhaps, best illuminated by a quotation from a work by Poe (1948): "The microscopic morphology of Boeck's sarcoid and Koch's tuberculous tissue is practically of the same pattern. In fact, so closely does one resemble the other that if a microscopic slide of either is shown to a good general pathologist he will unhesitatingly say that it is either one or the other, but will not commit himself by adherence to either without further clarifying information." According to this view then, the microscopical diagnosis of l.b. must be supported by characteristic symptoms. A microscopical diagnosis of this sort will, however, suffer from a considerable deficiency in that l.b., as we now know, may often run its course for many years with but few symptoms. The position of the pathologist is particularly difficult in that it is in just such cases that the clinician calls upon his assistance.

The differential diagnostic problem is certainly greatly simplified if one accepts the view put forward by Mylius and Schürmann, among others, that l.b. is also an atypical form of tuberculosis, more precisely, a generalised form of Ziegler's large-celled hyperplasia. This view has, however, not won general acceptance and, as has been mentioned in the introduction, the relation between l.b. and this type of tuberculosis forms the central question of the present work.

Another disease which may cause difficulty in differential diagnosis is *syphilis*. Miliary gummata may sometimes look very much like the granulomata of l.b. Even though the microscopical differentiation between l.b. and syphilis may sometimes be difficult, the history of the illness will usually be a good guide.

In countries where *leprosy* is prevalent a difficulty may arise in distinguishing it from l.b. As leprosy has almost died out in Sweden the differential diagnosis between it and l.b. will not be discussed further.

The microscopical differentiation between l.b. and *lymphogranuloma inguinale* may sometimes present difficulties, but this condition may usually be distinguished by the presence of extensive areas of purulent disintegration which are not found in l.b.

Certain difficulties may also arise in differentiating between l.b. and some *mycotic diseases* such as coccidioidomycosis, histoplasmosis and moniliasis. The lesions in these conditions are, however, usually more polymorphic than those in l.b.; there is also a pronounced tendency to a macrophage reaction and abscess formation and the fungi responsible can usually be easily demonstrated in the sections.

CHAPTER 5

Etiology

According to the views put forward in the literature l.b. is:

1. a virus disease (Zieler, 1909; Kuznitzky and Bittorf, 1915; Kissmeyer and Nielsen, 1933, and others;
2. syphilitic (Stillians, 1921);
3. caused by the lepra bacillus (Rabello, 1936; Saenz and Palomino, 1939);
4. a mycosis (Danlos and Bloch, 1901; Hollström, 1945; Törnell, 1946);
5. an allergic condition (Harrell, 1940; van Rijssel, 1947; Teilum, 1948, 1949);
6. a form of tuberculosis (Boeck, 1905; Kyrle, 1914; Jadassohn, 1919; Lewandowsky, 1921; Schaumann, 1936; Pinner, 1937; Leitner, 1942; Vogt, 1950; Schmid, 1951; Wätjen, 1952, and others).

Diverging opinions as to the etiology are also to be found in the current textbooks. While in German works l.b. is included under the heading of tuberculosis, the English and American books usually treat it as a disease *per se* and describe it under the name of sarcoidosis. Concerning the etiology Stainsby (1942), for example, says in Cecil's *Textbook of Medicine:* "The etiology of this condition [l.b.] has never been definitely established although many facts point to the tubercle bacillus as the causative agent." In *A Textbook of Pathology*, Moore (1945) writes: "The similarity of the lesion to that of tuberculosis has led many to believe that sarcoid is some atypical form of tuberculosis (Pinner). However, until tubercle bacilli can be demonstrated with more regularity, it is best to withhold judgement." Finally, Boyd (1944) formulates his opinion as follows: "The etiology is unknown. It has been suggested that the disease is an atypical form of tuberculosis without caseation, but it seems more probable that it is a chronic granuloma produced by some hitherto undiscovered agent."

Among the theories enumerated above, those concerned with syphilis and leprosy do not seem to be well founded and enjoy no support at present. They will therefore not be discussed further.

The Virus Theory

Perhaps the most important support for the virus theory is the fact that, in the great majority of cases of l.b., no responsible bacteria can be demonstrated. Further, similarities between it and certain virus diseases have been adduced in support of the virus theory. For example, in both

l.b. and certain virus diseases such as measles, there is a tendency to leucopenia and to weakening of the tuberculous allergy. Studies designed to demonstrate the hypothetical virus have been made by Löfgren and Lundbäck (1950) and by Robinson and Pound (1950). The results were negative, however.

The Mycotic Theory

The theory that l.b. is a mycosis was first launched by Danlos and Bloch (1901) and was later taken up again by Hollström (1945). He then reported that he had found both acid-fast rods and fungus-like rounded or oval corpuscles in a lymph node from a patient suffering from l.b. The tissue lesions corresponded very well with those seen in this disease. The fungus-like corpuscles lay mainly in the lymphoid tissue between the tuberculoid foci. As to their nature he wrote: "No doubt of these cells being of fungus nature does exist, as in a number of them there are clearly pronounced buds." His opinion as to relationship between the fungus cells and the acid-fast rods Hollström expressed as follows: "[Nor does] anything argue against the assumption that the acid-fast rods in L.B. have arisen from fungoid elements."

In 1946 Törnell again took up the mycotic theory and stated that there was a lot to suggest that l.b. was a chronic form of moniliasis due to exposure to dust containing monilia. He seems to have reached this conclusion by two approaches. On the one hand, considering his series of patients suffering from thresher's lung (pulmonary moniliasis), he was able to demonstrate that, in some respects, there was a great similarity between this disease and l.b. Thus it was very difficult to distinguish the radiographic pulmonary changes in moniliasis from those seen in certain stages of l.b. Further, he found that patients suffering from moniliasis were tuberculin negative to a greater extent than would be expected from their ages. He also observed that tuberculin negative patients suffering from pulmonary moniliasis remained tuberculin negative after BCG vaccination, as also do many tuberculin negative patients with l.b. (Lemming, 1942). From the other approach, he found that even in his series of l.b. there was sometimes a history of exposure to fungus-containing dust. According to Törnell, all these facts indicated that the two diseases were of the same origin.

The Allergic Theory

The allergic theory is mainly based on certain similarities between l.b. and some diseases which are, at present, supposed to be allergic (e.g. rheumatic fever, periarteritis nodosa and lupus erythematosus). According to van Rijssel (1947) the following observations favour the allergic theory:

1. the occurence of transient joint pains at the onset of the disease;
2. the not infrequent occurrence of eosinophilia in the blood;
3. the appearance of erythema nodosum in the earliest stages of the disease;
4. the presence of eosinophil leukocytes in the young granulomata;
5. the occurrence of rheumatic nodules in the heart showing a smooth transition to epithelioid cell granulomata; and
6. the occurrence of granulomata in the walls of the vessels.

As for the nature of the allergen, Harrell (1940) suggested that it might be lipids of bacterial origin, while van Rijssel identified it with the tubercle bacillus.

As has been mentioned, Teilum (1948, 1949) has also given his support to the allergic theory. According to him the presence in l.b. of concentric hyaline bands in the margins of the granulomata, periarterial hyalinosis and numerous plasma cells around the granulomata, as well as a weak or negative tuberculin reaction, can all be explained on the assumption that, in this condition, there is an allergic hyperglobulinosis of the reticuloendothelial system, determined by persistent or repeated stimulation of the immune mechanisms. Concerning the nature of the allergen he states that "the morphogenetic interpretation of the alterations in Boeck's sarcoid ... may easily be made to agree with the prevailing view of tuberculosis and Boeck's sarcoid as two phases of the same disease." Thus, as some workers identify the allergen with the tubercle bacillus, the allergic theory overlaps to a certain extent the tuberculous theory.

The Tuberculous Theory

While most authors support the view that l.b. is a tuberculous disease, there are many who oppose this view. There has been a long war of words between the upholders of these two points of view. It is remarkable that many workers who originally either opposed the tuberculous theory or were very cautious in their advocacy of it, gradually came to adopt it. Thus, for example, Leitner (1946) says: "Als wichtigste Argumente gegen die tuberkulöse Genese der Krankheit gelten die häufig negativen Tuberkulinreaktionen und die negativen Bazillenbefunde, die uns zu einer vorsichtigen Stellungnahme in unserer Monographie (1942) veranlasst haben, wenn wir auch betonten, dass es nicht anginge, sämtliche positiven Befunde als Versuchsfehler zu deuten. In den letzten 3 Jahren haben wir unsere Untersuchungen fortgesetzt und dabei Befunde erheben können, welche die gegen Tuberkulose ins Feld geführten Argumente abschwächen und überdies als Stützen der spezifischen Aetiologie angesehen werden können." Perhaps there is a certain truth in the remark of Schaumann (1937) that one is apt to reject the tuberculous theory when one *begins* to study the disease.

The strongest opponents of the tuberculous theory are certainly to be found among the clinicians. One of the reasons for this is that, from a purely clinical point of view, l.b. is unlike the acknowledged forms of tuberculosis. Thus Darier (1903), who became later a supporter of the tuberculous theory, said, in a talk on l.b.: "Eine solche Tuberkulose, die so grosse, mächtige Läsionen hervorbringt, welche rückgänging werden, bis sie ganz flach sind, ja vollständig schwinden, um durch andere anderswo auftretende remplaziert zu werden, alles ohne jemals zu ulzerieren, eine solche kennen wir nicht." Clinicians are also perplexed by the fact that the l.b. patients do not usually come from tuberculous families and that the source of infection can seldom be traced (Törnell, 1948). Another of the greatest stumbling blocks is the low sensitivity to tuberculin which is so often found in patients with l.b. This, according to the opponents of the tuberculous theory, is clear evidence against the tuberculous etiology of the disease.

Also among bacteriologists and pathologists there are several workers who, for various reasons, definitely reject the idea that l.b. is a tuberculous disease. The fact that guinea pig tests usually give negative results is the commonest argument adduced by the bacteriologists against the tuberculous theory, and not much significance is attached to the relatively few positive tests which have been reported. They are often dismissed as being sponaneous infections in the test animals (Kissmeyer, 1932; Zieler, 1939). As regards the pathologists, the difficulty of demonstrating acid-fast rods in tissue sections from cases of l.b. has been one of the reasons why some of them have been unable to accept the theory that the disease is of tuberculous origin, the more so because, as is well known, the human organism reacts locally to different agents with the formation of tuberculoid lesions (Nickerson, 1937, and others). The relatively few cases of l.b. in which acid-fast rods have been demonstrated in tissue sections have not been considered convincing either because the possibility of a mixed infection with tuberculosis could not be ruled out, or because there was always the possibility that the acid-fast bacilli were saprophytes. Bergstrand (1937), among others, put forward this suggestion in his statement: "Even if genuine tubercle bacilli were to occur in the lymph nodes in l.b. it would not prove anything, for tubercle bacilli also flourish in damaged lymphoid tissue, as experience with lymphogranulomatosis maligna shows."

As regards the arguments in favour of the tuberculous theory many authors have made clinical observations which they consider to suggest that l.b. is of tuberculous nature. For example, Schaumann (1934) was able to demonstrate the interesting phemomenon that if ordinary tuberculosis develops during the course of l.b. the lesions of this disease may disappear completely and the negative tuberculin reaction become positive. Similar observations have been made by Bonnevie and With (1937), Rist *et al.* (1937), Thomas (1943), Ricker and Clark (1949), and

others. This peculiar disappearance of the l.b. lesions during the development of an ordinary tuberculous process forms, as Schaumann (1937) maintained, a parallel with what we know in cases of lupus vulgaris and tuberculides. According to him it is therefore natural to suggest a common etiology of l.b. and tuberculosis.

As already stated, some authors maintain that patients suffering from l.b. do not usually come from tuberculous families and that it is exceptional to be able to trace the source of infection. They also point out that patients with l.b. seldom present signs of former tuberculosis. However, certain of the supporters of the tuberculous theory take the contrary view. Thus, for example, Vosbein and Bonnevie (1940) state that, of their 34 cases of l.b., 16 had certainly been exposed to tuberculous infection. Nine of these 16 patients had a family history of tuberculosis, two showed signs of previous pulmonary tuberculosis while seven others showed calcified primary foci. One of these last also showed radiographic signs of previous pleurisy. Several American authors have had similar experiences.

Another circumstance which is often adduced by clinicians in support of the view that l.b. is a tuberculous condition is the fact that it is not unusual for l.b. and classical tuberculosis to be concurrent. Thus there are cases described in which tuberculosis developed into l.b. (Storck, 1948; Leitner, 1949, and others). The opposite is, however, more common, namely that tuberculosis of the ordinary type develops in a patient suffering from l.b. (Schaumann, 1937; Rist *et al.*, 1937; Bjørnstad, 1948; Ricker and Clark, 1949, and others). As Bachmann (1947) pointed out, the development into ordinary tuberculosis is usually not gradual but sudden. In such cases the tuberculous process often takes the form of miliary tuberculosis (Ronchese, 1942; Ehrner, 1946; Frey, 1948; Müller and Pedrazzini, 1948; Leitner, 1949; Ricker and Clark, 1949). As has previously been mentioned, the sensitivity to tuberculin then usually rises. This is particularly well illustrated by an observation of Leitner (1946). In association with the development of ordinary tuberculosis in a patient with l.b., marked reddening of the skin occurred at the sites at which tuberculin had been injected some weeks before with negative results.

The fact that the tuberculin reaction is often negative in l.b. has naturally been a stumbling block for the supporters of the tuberculous theory. They have been forced to invoke several additional hypotheses to explain this phenomenon. Thus Jadassohn (1919) has tried to explain the anergy to tuberculin in l.b. as a "positive anergy". According to him the formation of antibodies is followed by the production of anticutins in the serum which diminish the tuberculin reaction. Some workers (e.g. Martenstein, 1921) have even thought that they could demonstrate such anticutins in the serum in l.b., while others have not been successful in doing so. According to Schröpl (1943) Jadassohn's theory is supported by the observation of Lemming (1942) that BCG vaccination of patients suffering from l.b. does not always evoke allergy

in spite of the use of large doses of vaccine. Teilum (1948) also considers himself able, on the basis of his own investigations, to accept Jadassohn's theory of positive anergy in l.b. as an expression of a high degree of immunity and quotes his statement that the organism tackles the tuberculin so rapidly that no reaction, or only a faint one, appears. In accordance with his view that l.b. is a form of tuberculosis, Leitner (1949) suggests that the antibodies are bound at the site of their formation, i.e. the reticuloendothelial system, by break down products of tubercle bacilli. According to him the fact that the tuberculin reaction is positive in some cases of l.b. may be explained by supposing that this binding is sometimes incomplete. Uehlinger (1942) and several others, who support the tuberculous theory, consider that the hyposensitivity to tuberculin is constitutional. The idea that constitutional factors play a part in determining the character of tuberculosis is based on the experience that the defensive reactions of the organism have been found to be constitutionally determined. The suggestion that l.b. is the response to tuberculous infection of a particular type of constitution, is supported by the observations of several workers that the disease may be familial.

As far as the histopathology of l.b. is concerned, the suporters of the tuberculous theory have put forward the remarkable fact that, as Vogt (1950) says, "weder morphologisch noch pathogenetisch ein absolut sicheres, von bekannten Tuberkulosebildern abweichendes Merkmal angegeben werden kann". Many authors consider this fact to be a strong support for the tuberculous theory.

Even though the demonstration of tubercle bacilli in l.b. is not usually successful there are, however, several cases reported in which acid-fast bacilli have been found by microscopical examination of the granulomatous tissue, or in which genuine Koch's bacilli have been demonstrated by culture and guinea pig tests. These observations have been collected in Tab. 1. However, as already stated, different authors give different values to them. Although some workers try to minimise their value, the supporters of the tuberculous theory maintain that even sporadic findings of acid-fast rods or genuine Koch's bacilli must be significant in the assessment of the etiology of l.b. Thus, for example, Kyrle (1921) writes: "Der Grundsatz, dass ein einzig sicher positiver Befund mehr zu sagen habe als zahlreiche negative Fälle, wurde merkwürdigerweise nicht entsprechend anerkannt." Furthermore, present-day writers can point to the fact that these sporadic findings are now not so few (Schröpl, 1943). Further, when some authors maintain that the positive results in guinea pig tests are due to experimental errors, the supporters of the tuberculous theory counter this criticism with the argument that the observations were made by experienced workers of sound judgement. Thus, for example, Sulzberger (1933) writes: "Suffice to say that any attempt to deny the tuberculous aetiology of sarcoids would represent a decided step backward and a denial of the conclusions reached through years of study and experiment by trained observers."

Table 1. Synopsis of reported cases of l.b. in which acid-fast bacilli were found or positive results obtained by culture or guinea pig test.

Case no.	Year	Author	Tissue studied	Direct observation	Culture	Guinea pig test	Comments
1	1905	Boeck	nasal mucosa	pos.		pos.	Animal killed 3 mo. after injection. Only local lesions and regional adenitis with "sarcoid-like" picture.
2	1910	Kyrle	skin	neg.	neg.	pos.	Animal died 10 mo. after inoculation. Tuberculous abscess at site of injection and regional adenitis. Generalised tuberculosis. Three other animals inoculated with the same material showed no sign of tuberculosis.
3	1914	Schweitzer	skin	neg.	neg.	pos.	"Healed tuberculosis" in the omentum of the animal 10 weeks after intraperitonal inoculation.
4	1917	Secrétan	spleen			pos.	
5	1920	Jüngling	bone marrow	neg.	neg.	pos.	One of the two animals inoculated died of generalised tuberculosis 7 mo. later. The other died of an intercurrent infection.
6	1920	v. Gebsattel	spleen	neg.		pos.	Generalised tuberculosis 7 weeks after inoculation. (Only one animal used.)
7	1920	Kyrle	skin	pos.		neg.	Bacilli only in early lesions. Negative guinea pig test using material containing acid-fast bacilli. (Four animals used.)
			blood			pos.	Animal died after 29 days. Generalised tuberculosis.
8	1921	Gans	skin			pos.	The two animals used were killed 7 weeks after inoculation. One showed regional adenitis and tuberculosis of the liver and spleen.
9	1922	Ruete	skin	pos.		neg.	Bacilli only in recent skin lesions. The inoculated animal died of an intercurrent illness.

							passage through three animals. Bovine type of tubercle bacilli.
11	1924	Schaumann	sputum			pos.	Sputum inoculated into 8 guinea pigs: 7 remained healthy. One died after two months, presenting hyperplastic nodes without tubercles. Inoculation of a guinea pig with material from such nodes gave rise to fibrous tuberculosis.
12	1925	Hudelo, Montlaur and Leforestier	skin	pos.		pos. (?)	A small number of bacilli in the skin lesions. Regional adenitis in the test animal. One acid-fast rod seen.
13	1925	Keck and Michalik	lung tissue			pos.	The animal did not die till 161 days after inoculation. Generalised nodular tuberculosis. Bacilli of human type. Considerable increase in virulence after several animal passages.
14	1927	Krupnikoff	skin	pos.			Numerous bacilli in the early skin lesions only. In the older ones "Bazillen nur in einzelnen von vielen Dutzenden Präparaten".
15	1927	van der Hoeve	lymph node		?	?	The method by which tubercle bacilli were demonstrated in the node is not stated.
16	1928	Cavara	lachrymal gland			pos.	Only one of several inoculated animals died of tuberculosis of the lungs and liver.
17	1928	Watanabe and Mariyama	skin	pos.		neg.	
18	1929	Souter	heart muscle	neg.		pos.	
19	1929	Mylius and Schürmann	lymph nodes	neg.	neg.	pos.	Two out of five inoculated animals died of generalised tuberculosis. Tubercle bacilli of human type.

(Table 1 contd.)

Case no.	Year	Author	Tissue studied	Direct observation	Culture	Guinea pig test	Comments
20	1933	Stalmann	bone marrow		neg.	pos.	Tuberculosis only in the regional nodes in the animal inoculated subcut. Diffuse, miliary peritoneal scattering of tubercles in that which was inoc. intraperit. Acid-fast rods were only seen in the former animal. Virulence could not be augmented by repeated guinea pig passage.
21	1934	Tanner and McCurry	parotid gland			pos.	
22	1934	Ramel	skin			pos.	Fatal tuberculosis produced only after three passages. Tubercle bacilli of bovine type.
23	1934	Sannicandro	skin			pos.	
24	1936	Pautrier and Glasser	skin	neg.		pos. (rabbit) neg. (guinea pig)	Clinically a typical case of l.b. but microscopically "une structure plus tuberculoïde que de coutume". Regional adenitis only in the rabbit.
25	1939	Berblinger	lymph node	neg.		pos.	The guinea pig was killed 6 weeks after inoculation and a tubercle was demonstrated microscopically in a lymph node. Inoculation of a guinea pig with material from this node produced tuberculosis. In spite of an exhaustive search no acid-fast rods could be found in the sections of the node.
26	1939	Ishikawa	skin		pos. (Petragnani's medium)	pos.	Tuberculous regional adenitis in the test animal. Tubercle bacilli of bovine type.
27	1939	Leder	skin			pos.	Enlarged inguinal lymph nodes in one of the two animals inoculated. Culture of these nodes gave growth of tubercle bacilli.

29	1940	Nicolas and Gaté	blood		pos. (microculture on Loewenstein's medium)		
30	1941	Yamazaki and Harada	skin	pos.		pos.	Tubercle bacilli of human type.
31	1941	Yamazaki and Harada	skin	pos.		pos.	
32	1941	Schaumann and Hallberg	lymph node	pos.		neg.	
33	1943	Schröpl	skin	neg.	pos.		Growth of tubercle bacilli was only obtained in 3 of 8 tests. The material for all these 3 tests was obtained from recent lesions.
34	1943	Schröpl	skin		pos.	neg.	In this case as in case no. 34 Petragnani's medium was used. Tubercle bacilli of human type.
35	1945	Hollström	lymph node	pos.			
36	1946	Granström, Gripwall, Kristofferson and Lindgren	lymph node	pos.		pos.	
37	1949	Rosenthal	hilar lymph nodes	neg.	neg.	pos.	A large number of animals were inoculated and died of generalised tuberculosis. Numerous acid-fast rods in their organs. Cultures of these were negative for tubercle bacilli. The lesions of the test animals closely resembled l.b.
38	1949	Ricker and Clark	lymph node			pos.	Small necrotising foci containing acid-fast bacilli in the spleen and liver of the animals.

CHAPTER 6

The Problems. Aim of the Investigation

The review of the literature thus shows that opinions are divided as to the etiology of l.b. It is remarkable that, as far as the tuberculous theory is concerned, some workers support it enthusiastically while others oppose it with equal energy. The different attitudes towards the tuberculous hypothesis also appear in different views concerning the relationship between l.b. and the large-celled hyperplasia described by Ziegler. Thus, some workers consider that they are quite distinct. Others, on the other hand, consider that the clinical concept of l.b. corresponds to the histopathological term large-celled hyperplasia. The obscurity of the relationship between l.b. and Ziegler's hyperplasia may be seen from the statement of Gravesen (1942): "In Ziegler's work of 1890 the illustrations of the large-celled hyperplasia show a strong resemblance microscopically to l.b. It would, however, be going too far to call *all* lymph nodes with this structure l.b., as it has been shown that very chronic tuberculosis may present the same picture." Further, Robb-Smith (1938) stated: "This condition (the large-celled hyperplasia of Ziegler) resembles a diffuse chronic granulomatous tuberculosis, and Ziegler actually claimed to have found tubercle bacilli in it. There is, however, considerable evidence against its being tuberculous (Longcope & Pierson, 1937) and I shall use the non-committal term 'sarcoidosis' suggested by these writers." This shows that if one wants to adopt a critical attitude towards the etiology of l.b. one must first clear up the relationship between this syndrome and the large-celled hyperplasia of Ziegler.

It should be possible to solve the problem of the relationship between Ziegler's large-celled hyperplasia and l.b. either from a clinical or histopathological starting point. The present author has chosen the latter approach and, as was stated in the introduction, started from a series of lymph nodes showing a fairly uniform tuberculoid microscopical picture. As the material was collected solely on the basis of the microscopic appearance, and as the picture in Ziegler's hyperplasia is very like that seen in l.b., one might expect that the series would contain lymph nodes affected by both conditions. Assuming that Ziegler's hyperplasia really is a form of tuberculosis the presence or absence of

acid-fast rods in the nodes might be used as a basis for division of the material. Such a division was gradually found to be justified. Thus, in some cases bacilli could be demonstrated, while in others they could not, although large series of sections were examined. The following question therefore became relevant: Do the two series represent completely separate diseases or only one disease, in spite of the absence of bacilli from some of the material?

This question made it necessary to analyse both of these two series carefully both from the clinical and the microscopical point of view. If the clinical analysis were to show that the symptoms of l.b. were only present in the series in which bacilli were not to be found it would suggest that l.b. is a disease *per se*. If they were also to be found in cases in which bacilli were demonstrated it would give strong support to the view that l.b. is of tuberculous origin.

The review of the literature shows that the tissue lesions in l.b. are characterised by a number of details to which great significance has been attached for the differentiation of it from tuberculosis. Supposing that the series of lymph nodes in which bacilli were found and that in which they were not demonstrated represent two separate diseases, these characteristic microscopical details should be present only in the series in which the bacilli were not found. On the other hand, if they were equally distributed through both series, it would give support to the idea that the etiology is the same in both.

On the basis of the results which analysis of the material along these lines might be expected to give it should be possible to form an opinion as to the relationship between l.b. and tuberculosis. An investigation of this kind might also contribute to the provision of a better basis for the difficult differentiation between l.b. and other microscopically similar affections, especially the Ziegler form of tuberculosis.

CHAPTER 7

Material and Methods

Nature of the Material

The main material in the present investigation consists of lymph nodes examined at the Pathological Institution in Uppsala in the years 1935–1952 and registered there as atypical tuberculosis (a.t.). To this were added some further lymph nodes showing a similar microscopical picture. Some of these were examined at the Pathological Department of Södersjukhuset in Stockholm (Head: F. Wahlgren, M.D.), and others at the Pathological Department of the Central Hospital in Västerås (Head: I. Behring, M. D.). These preparations were registered as l.b. The material also includes a few lymph nodes in which a first microscopical examination led to the diagnosis of tuberculosis but in which subsequent clinical data or examination of other lymph nodes from the same patient caused the pathologist to alter his diagnosis to a.t. or l.b.

The origin of the material is indicated by the signs S. (Stockholm), U. (Uppsala) and V. (Västerås).

The material is selected, inasmuch as lymph nodes in which there was only a small amount of granuloma tissue were not further investigated.

The investigation is, for the most part, confined to lymph nodes in order to obtain as uniform a material as possible. This has not, however, prevented the occasional use of other material in order to clarify particular points. The nature of such material is given in each particular case.

Primary Microscopical Diagnosis

In the great majority of the lymph nodes coming from Uppsala the microscopical diagnosis a.t. has been used. In some cases, however, it has been given as l.b. This occasional deviation from the habit of using the term a.t. cannot be referred to any significant difference of the microscopical picture but seems simply to be an indication of the belief of the pathologists that the histopathological term a.t. corresponds to the clinical term l.b.

Microscopical Analysis

Most of the material has only been available in the form of paraffin blocks. In some cases, however, it has been possible to obtain lymph nodes for making frozen sections. In addition to the routine staining methods with hematoxylin-eosin and hematoxylin-picrofuchsin (van Gieson), a number of other staining methods have been used to demonstrate particular structures. These are mentioned each time they were used.

The Ziehl-Neelsen method has been used as a routine for the demonstration of acid-fast bacilli but the method of Hallberg (1941) using Nachtblau stain has occasionally been used.

Clinical Analysis

The author has had access either to the original case notes or to copies of them for the clinical analysis. As these did not give all the information which was required an effort was made to trace all the patients, and those who could be traced were sent a letter. This work was mostly done in the end of 1951 and the beginning of 1952. This follow-up letter was designed to find out whether the patient had been in close contact with persons suffering from tuberculosis and also whether he or she had had any further symptoms suggesting tuberculosis or l.b. since the examination of the lymph nodes.

Division of the Material

The search for bacilli was prosecuted with great diligence and in no case was a negative finding recorded until a large number of sections had been examined. The author, therefore, feels justified in using the presence or absence of bacilli as a basis for dividing the material into following two series:

Series I comprising lymph nodes in which bacilli were found (59 specimens from 58 patients) — *tuberculosis chronica hyperplastica* (Ziegler's large-celled hyperplasia).

Series II comprising lymph nodes in which bacilli were not found (53 specimens from 50 patients) — *lymphogranulomatosis benigna*. In cases 21 and 28 nodes were also obtained in which bacilli were demonstrated.

CHAPTER 8

Series I

Lymph Nodes With Bacilli Present. Tuberculosis Chronica Hyperplastica

(*Case Reports see pp. 132—150*)

Age and Sex Distribution

Of the 58 patients 31 are women and 27 men. The youngest is 10 and the oldest 76 years old. The age distribution is as follows:

10–19	years	9	cases	50–59	years	12	cases
20–29	»	4	»	60–69	»	7	»
30–39	»	15	»	70–79	»	3	»
40–49	»	8	»				

Clinical Picture of the Lymphadenitis

As the case histories show it is a single or a few adjacent lymph nodes which are affected in the great majority of cases. There were, however three cases (1, 18, and 49) in which peripheral lymphadenitis was found in widely separated sites while, in two others (46 and 50) the enlargement of the lymph nodes was almost universal.

A characteristic feature of the clinical picture is that the swelling of the lymph nodes has usually lasted a long while, often several years, and that it was only in relatively few cases that the clinician received the impression that it was tuberculous in nature. This was partly due to the long duration but also to the absence of periadenitis, the firm consistency of the enlarged nodes and the appearance of their cut surface which appeared greyish yellow, sometimes greasy and finely granular without the slightest sign of caseation. Although the clinical diagnosis of tuberculous lymphadenitis is not completely absent from this series it is remarkable how often the clinicians expressed the suspicion that some other condition might be present in these cases, e.g. salivary gland tumour, branchial cyst, Hodgkin's disease or malignant tumour.

Fig. 1 (Case I: 9). Bilateral hilar enlargement.

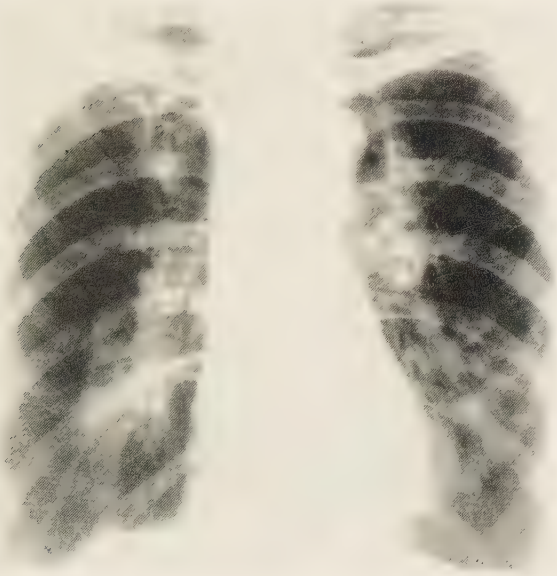

Fig. 2 (Case I: 26). Bilateral hilar enlargement with ring-shaped areas of calcification in some places. Bilateral streaky opacities of the parenchyma.

Fig. 3 (Case I: 52). Bicyclically demarcated enlargement of the left hilus.

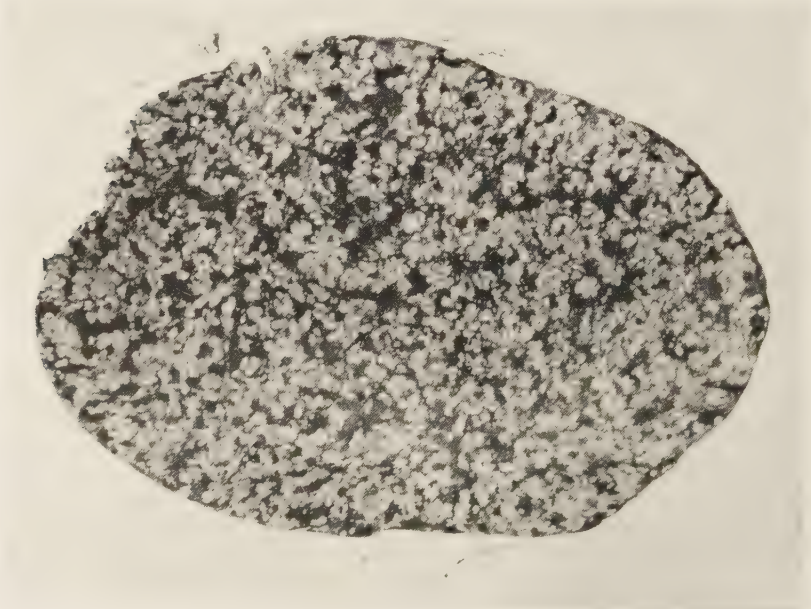

Fig. 4 (Case I: 45). Lymph node showing the pattern characteristic of series I. — Htx.-v.G.

Clinical Relationship to Classical Tuberculosis

Even though the affection of the lymph nodes does not conform to the classical picture of tuberculous lymphadenitis, the clinical analysis of the material reveals certain features which suggest that this may be a tuberculous process. Thus, tuberculous heredity was recorded in 11 of the 43 cases (25.6 per cent) in which reliable information could be obtained on the matter.[1] Furthermore, eight of the 38 patients whose lungs were X-rayed (21.1 per cent) showed calcification in the lungs or hilar lymph nodes as signs of previous tuberculous infection. In 11 cases (19.0 per cent) there was a previous history of manifest tuberculosis. In four of these cases the present affection of the lymph nodes was a relapse from a classical tuberculous lymphadenitis with approximately the same localisation. Only two patients had previously been treated in a sanatorium for pulmonary tuberculosis.

It is remarkable that in only one case (32) did any manifestation of classical tuberculosis appear between the operative removal of the lymph nodes and the follow up investigation, although the average interval was more than five years. None of the 31 patients traced has died of tuberculosis.

Clinical Relationship to l.b.

In seven cases an active pulmonary process of a clinically obscure nature was found at the time when the lymph nodes were removed. In five of these (2, 9, 26, 56 and 58) it took the form of bilateral hilar enlargement (Figs. 1 and 2), while in a sixth (52) the hilar enlargement was unilateral (Fig. 3). In one of the bilateral cases (26), the hilar enlargement was found to be associated with bilateral pulmonary lesions which looked suspiciously like those of l.b. In the seventh case (31) the pulmonary changes only took the form of a bilateral, symmetrical, fine, streaky speckling such as is seen in l.b. It is remarkable that both of the cases in which there were bilateral lesions in the pulmonary parenchyma were tuberculin negative using 1 mg tuberculin and that in case 58 this was the lowest dose at which a positive reaction was obtained. This was so in case 48 too. The rest of the patients who were tuberculin tested gave relatively strong positive reactions. Four of the cases showed monocytosis (normal values 5–6 per cent) and in both the cases in which a serum protein determination was made hyperglobulinemia was found.

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[1] Tuberculosis heredity is recorded in cases where parents, brothers or sisters had suffered from tuberculosis.

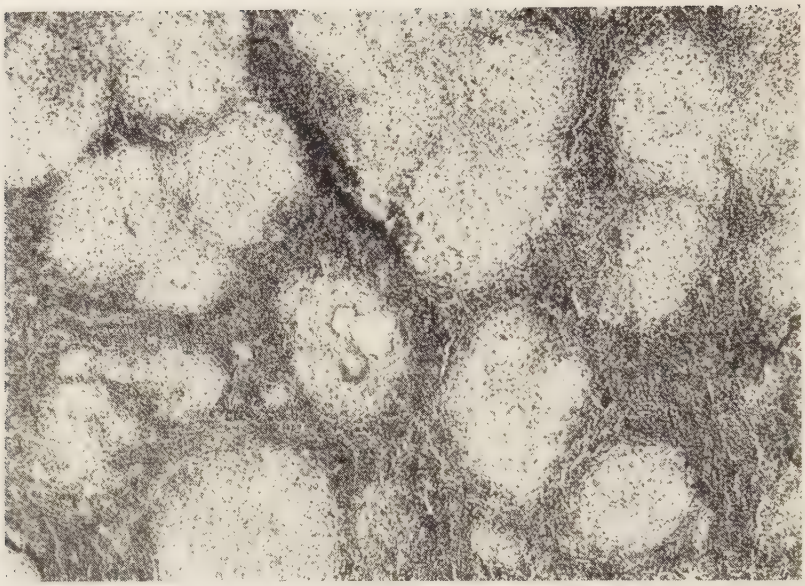


Fig. 5 (Case I: 23). Lymph node with miliary non-caseating tubercles arranged in groups. Few giant cells. A couple of Schaumann bodies in the middle of the picture. Htx.-v.G.

No further clinical relationship to l.b. could be demonstrated. In the cases in which radiography of the bones of the hands and feet was undertaken it showed no noteworthy changes.

It seems that no symptoms of l.b. have appeared in any of the patients in the interval between the extirpation of the lymph nodes and the follow up.

Microscopical Picture of the Lymphadenitis

General Pattern

The great majority of the lymph nodes in this series are distinguished by a characteristic pattern which is best seen by using low magnification. The lymphoid tissue will then be seen to be fairly uniformly scattered with submiliary-miliary rounded foci, fairly uniform in size and composed of epithelioid cells with a small admixture of Langhans giant cells. Characteristically, the tubercles are arranged in trefoil or rosette-like formations with small areas of intact lymphoid tissue between. This grouped arrangement of the tubercles is usually present throughout the

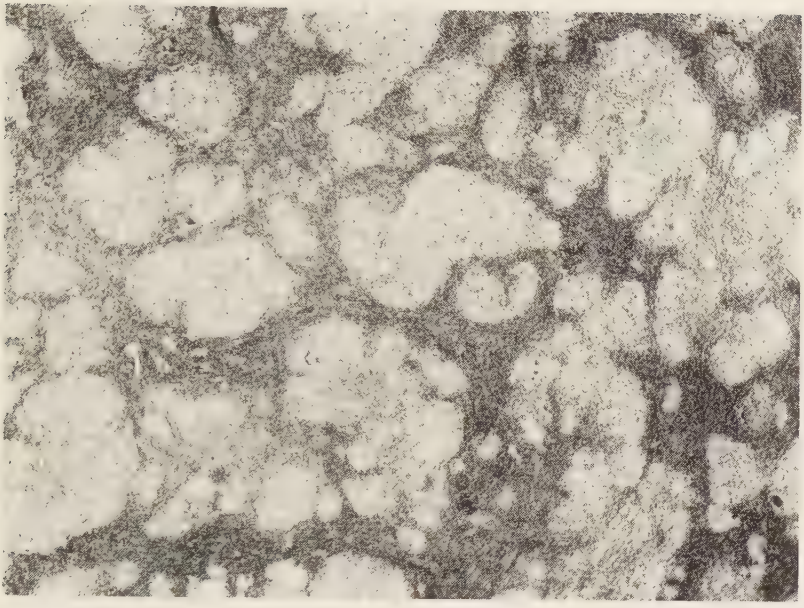


Fig. 6 (Case I: 20). Lymph node with miliary-submiliary tubercles arranged in groups with few giant cells and no caseation. Htx.-v.G.

whole node and gives it its characteristic pattern as mentioned above, the light conglomerations of granulomata contrasting with the deeply staining intact parenchyma of the lymph node (Figs. 4 6). The slight or moderate tendency of the foci to coalesce is also characteristic. The tubercles often lie in contact with the capsule of the node but it is only in exceptional cases that they break through it.

It might, perhaps, be thought that the fact that the conglomerates of tubercles lie in isolation, separated from each other by intact lymphoid tissue, was due to the process being in a relatively early stage and that, in a more advanced stage, it would affect the whole of the lymphoid parenchyma. It would appear, however, that this is not so. The same pattern is characteristic of nodes which have been enlarged for several years before being excised as for those excised relatively soon after they became enlarged.

There is, however, a minor number of nodes in which this characteristic picture is absent, either because the adjacent tubercles have coalesced to form larger units which are only separated by narrow bands of unchanged lymphoid tissue or because the parenchyma is diffusely scattered with uniform-sized granulomata, completely separated from

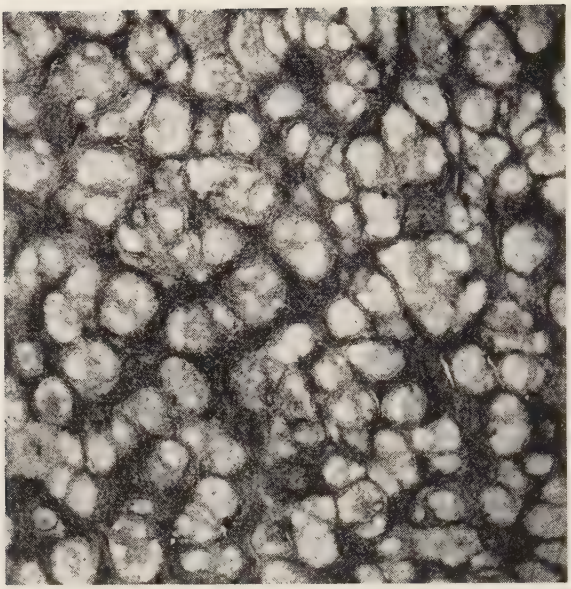


Fig. 7 (Case I: 31). Lymph node with fairly diffuse scattering of submiliary tubercles without caseation. Htx.-v.G.

one another and not lying close together. Cases 31 (Fig. 7) and 56 are typical examples of this latter pattern which is commoner in series II.

The Epithelioid Cells

The epithelioid cells differ morphologically from those seen in classical tuberculosis. They are, in general, larger. The nucleus is often peripheral and the cytoplasm usually contains the enlarged, pale staining or achromatic centrosphere. At low magnifications the presence of enlarged, pale staining centrospheres in the epithelioid cells gives the tubercles a peculiar structure, in which the centrospheres look like punch holes (Fig. 8). This is particularly striking in preparations stained with Heidenhain's iron hematoxylin.

On using a higher magnification the various details of the enlarged microcentrum appear, especially clearly when this iron hematoxylin method or azan staining is used. The acidophilic centrosomes are seen lying in the middle of the centrosphere, arranged either in a clump or in the form of a rod. A slender, slightly basophilic radial structure is seen within the sphere (Fig. 9). The individual rays are sometimes seen to be bound together by fine threads running parallel with the periphery of the spheres.

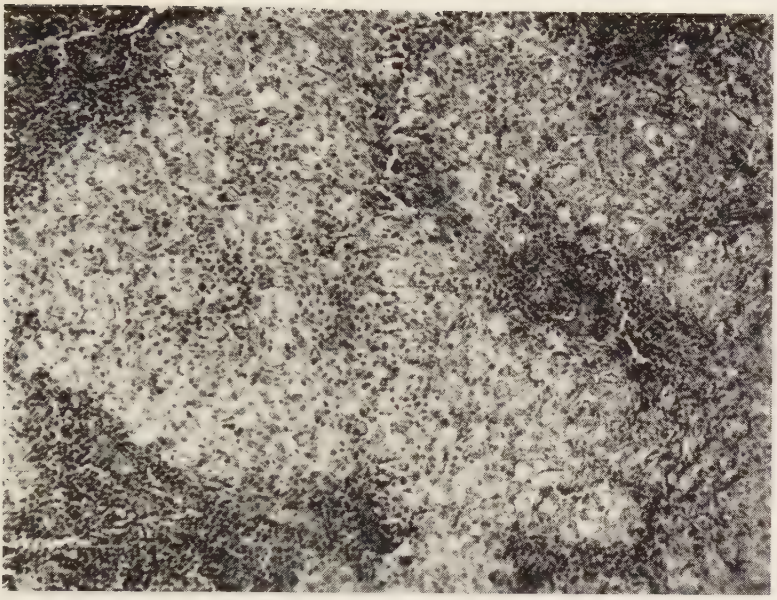


Fig. 8 (Case I: 15). Lymph node with two tubercles. The centrospheres of the epithelioid cells look like perforations in the section. Htx.-v.G.

The part of the cytoplasm which is not occupied by the centrosphere stains lightly with eosin and hematoxylin. When stained with pyronin by Unna's method, however, it sometimes takes on an intense red colour, a fact which according to some authors (e.g. Ehrich and Harris, 1949) indicates increased amounts of ribose nucleic acids.

As already mentioned, the nucleus of the epithelioid cells which contain an enlarged centrosphere is often situated peripherally. It is usually elongated in shape, curved, and lies with its concave surface in direct contact with a part of the surface of the sphere. The epithelioid cells often contain two or more nuclei, usually situated at opposite poles. Such large multinuclear epithelioid cells are transitional forms between ordinary epithelioid cells and Langhans giant cells. In this series it is rare to see mitotic figures in the epithelioid cells.

The Giant Cells

As has been mentioned above, transitional forms between epithelioid cells and Langhans giant cells exist in the form of multinuclear epithelioid cells. There may therefore sometimes be a certain difficulty, especially when using a high magnification, in deciding whether any

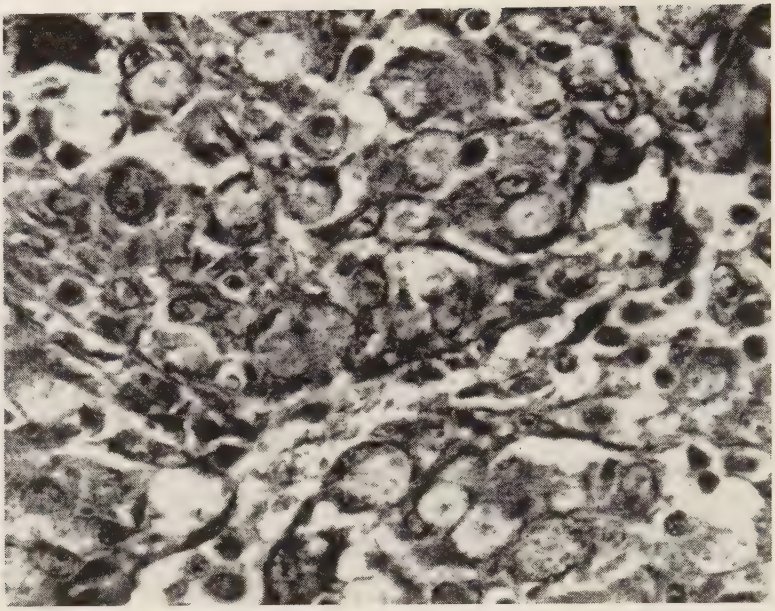


Fig. 9 (Case I: 15). Part of a tubercle with many enlarged microcentra. The centrosomes are seen in the middle of them. Distinct radial markings in the centrospheres. Heidenhain's azan staining.

given multinuclear cell should be described as a large epithelioid cell or a small Langhans giant cell. If a low magnification is used the differentiation is less difficult because the multinuclear epithelioid cells do not give the same impression of being giant cells when seen alongside the genuine Langhans giant cells. These occur very sparsely in the tubercles but are seldom absent. In some cases there are also giant cells which look more like foreign body giant cells than ordinary Langhans giant cells. These may occur in the tubercles themselves or may lie singly or in groups in the intervening areas. The nuclei are not bipolar or peripheral to the same extent as in the ordinary type of Langhans cells. Even if one takes into account the fact that, as has already been pointed out, the giant cells in tuberculosis are variable in both size and shape, one can hardly avoid describing them as atypical. These giant cells very often contain Schaumann bodies (Fig. 10).

The microcentra of the giant cells have the same morphological and staining properties as those of the epithelioid cells. While the small giant cells usually only contain one microcentrum the larger ones may contain two or three microcentra. These usually lie at the periphery of the cell and are considerably larger than those of the epithelioid cells.

Degenerative changes are common in the giant cells and may be seen

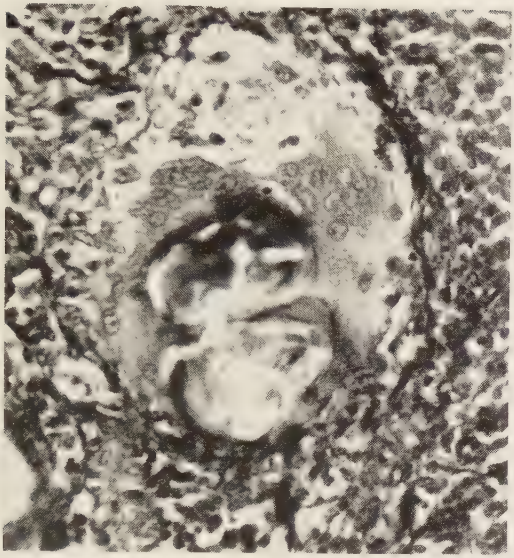


Fig. 10 (Case I: 56). Lymph node with an isolated giant cell (i.e. one not forming part of a tubercle) containing two concentrically laminated Schaumann bodies. Htx.-v.G.

in both the nuclei and cytoplasm. In the nuclei they manifest themselves as pyknosis and karyolysis while in the cytoplasm they take the form of a highly refractile granularity and a change in the staining properties. For example, in a preparation stained with azan the cytoplasm may often take on an intense red colour, which might be interpreted as being due to a physical change in the cellular protein. Even in preparations stained with pyronin there may be a greater or lesser degree of red staining of the cytoplasm. Sudanophil granulations are also sometimes seen in the cytoplasm.

The inclusion bodies

Although the term inclusion bodies is not very suitable as it easily leads to confusion with the intranuclear or intraplasmatic bodies which are seen in some virus diseases and are also often called inclusion bodies, the present author has felt bound to retain it nevertheless as it is almost universally accepted. The term foreign bodies which has been used by some authors for these formations, is, on the other hand, completely wrong as will be shown later.

In the study of the morphology, pathogenesis and mutual relationship of the asteroids and Schaumann bodies a case of granulomatous salpingitis has been used as well as the series of lymph nodes. It was investigated at the Pathological Institution in Uppsala in 1942.

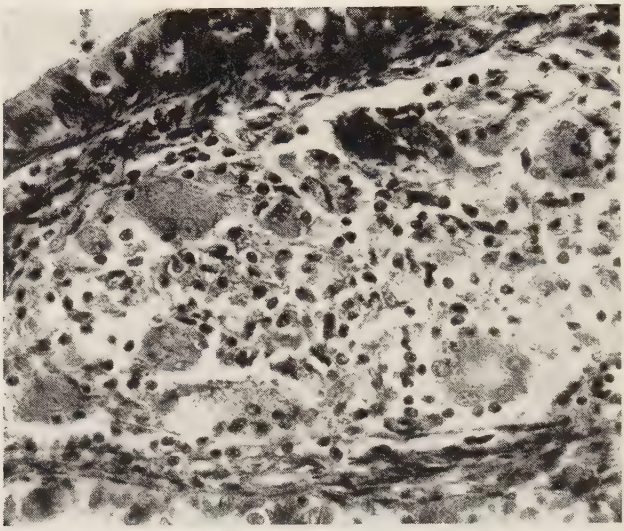


Fig. 11 (U. 825/42). Chronic hyperplastic tuberculosis of the Fallopian tube. A tubercle in a fold of the mucosa. No caseation. Many giant cells. Htx.-v.G.

Case report. ♀, born 1905. Patient attended the hospital for abdominal trouble. On examination the uterus was found to be enlarged. Salpingography was not performed. At operation the suspicion of myomatosis was confirmed. The tubes were found to be thick and swollen and filled with a thick greyish white material. *Microscopical examination U. 825/42* (Prof. Gellerstedt): The tubes show remarkable lesions. The picture is, in general, that of tuberculous foci in both the mucous and the outer layers of the walls of the tubes (Fig. 11). In the remnants of the lumen, between the folds of mucosa which have often grown together, there is a trace of purulent secretion. There is no definite caseation and, in spite of an energetic search, no tubercle bacilli. In several places in the granulomatous tissue there are groups of peculiar, concentrically laminated bodies which look like concremental deposits and are partially doubly refractile (Fig. 12). Some of them lie within giant cells of the Langhans type. On must seriously question whether this can be a case of tuberculosis, not so much because the bacteria were not to be found but, more particularly on account of the absence of caseation, the presence of foreign bodies and the absence of tubercles on the serosal surface. — Re-examination of the preparations by the present author showed that a large number of the giant cells also contained asteroid bodies. After time-consuming investigations two acid-fast rods were found in the granulomatous tissue.

THE ASTEROID BODY

Asteroid bodies are to be found in small numbers in three (5.2 %) of the cases. In all cases they are accompanied by Schaumann bodies.

A comprehensive description of the asteroid bodies will be found in Chapter 9.

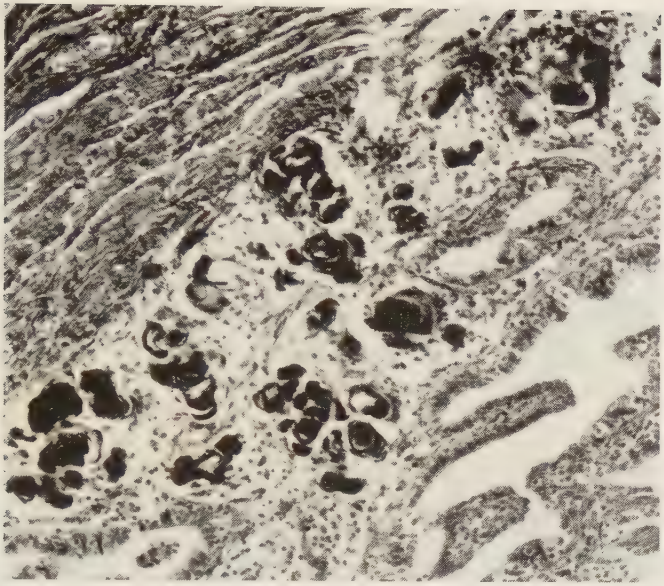


Fig. 12 (U. 825/42). Chronic hyperplastic tuberculosis of the Fallopian tube. Submucous tubercles with numerous Schaumann bodies. Htx.-v.G.

THE SCHAUMANN BODY

Schaumann bodies were found in larger or smaller numbers in 13 (22.4 %) of the cases in this series. They usually lie within giant cells and, as has been mentioned before, particularly often in those which lie singly or in groups in the lymphoid tissue without forming a part of a tubercle (Fig. 10). These bodies vary very widely in size. Some are hardly larger than a red blood cell while others have a diameter of up to 200 μ. A couple of small bodies may often be seen in the same cell (Fig. 13 a). While the smallest examples usually show no definite structure, the larger ones have, as a rule, a fairly regular, concentrically laminated arrangement around a centre which may be either structureless or star-shaped (Fig. 13 b).

The position of the Schaumann bodies in the cell varies. The larger ones not infrequently occupy almost all of the cell body so that one can only see a narrow rim of cytoplasm round the periphery which may contain some pyknotic nuclei (Fig. 13 c). Schaumann bodies are occasionally found lying free in the tissue.

The Schaumann bodies are anisotropic. This property is most conspicuous in the central parts. If the section is treated with acid, the anisotropy disappears because the inorganic substance in the bodies is

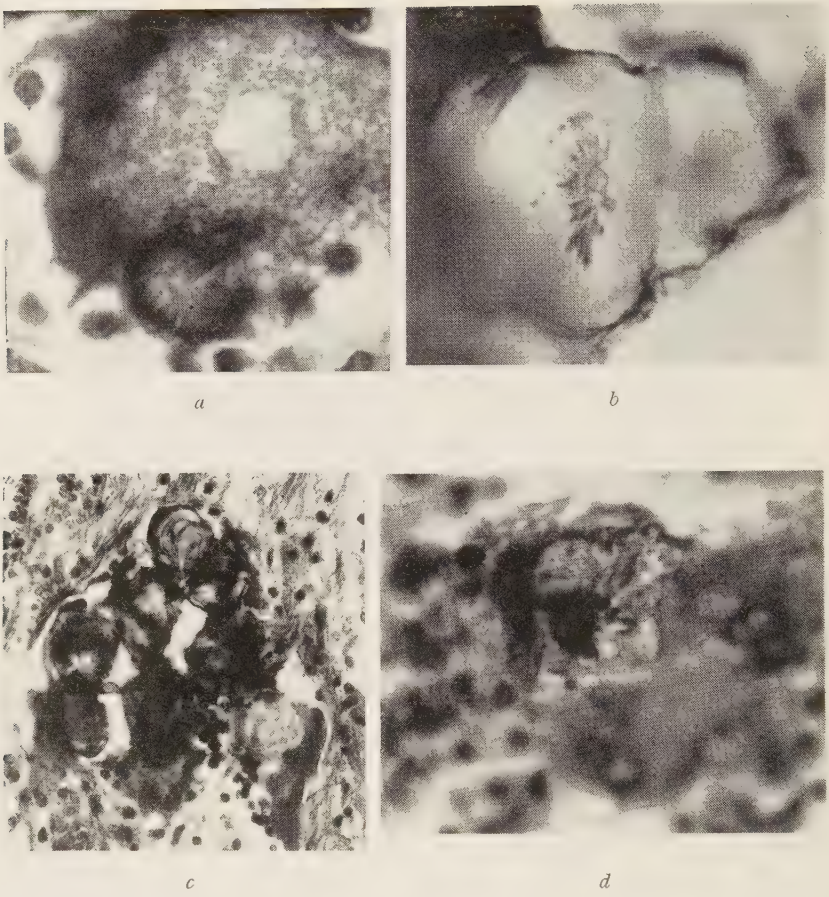


Fig. 13 *a*. Giant cell containing both a small structureless Schaumann body and a calcified asteroid body of about the same size. Both inclusions are anisotropic. Htx.-v.G. — *b*. A Schaumann body with well-defined concentric lamination. A star-shaped structure in the middle. Htx.-v.G. — *c*. Numerous Schaumann bodies surrounded by remains of giant cells. Htx.v.G. — *d*. Giant cell with a Schaumann body in the centre of which there is a dark (reddish brown when stained with orcein) mass which probably represents the remains of an asteroid body. Orcein-methylene blue. — All these photographs are from the case of tuberculous salpingitis (U. 825/42) described on p. 76.

dissolved. Gas is formed during this process. After treatment with acid only the whole or a part of the outer lamellae remain. These are obviously more firmly anchored to the rest of the giant cell and probably contain a greater amount of organic stroma than the more central parts.

The Schaumann bodies have no colour of their own. They take on a bluish grey or bluish black colour with hematoxylin. They give positive results with v. Kossa's reaction and the iron reaction. They do not stain with gentian violet or Congo red or with Gram-Weigert's fibrin stain. In sections stained with orcein an irregularly formed, structureless, brown substance is occasionally seen in the centre of the bodies (Fig. 13 d). However, the fragments of the organic stroma which remain after decalcification do not usually have the staining properties of elastin. In azan stained preparations the effect of acid treatment is manifested in partial solution of the bodies. Isolated threadlike structures, representing the remains of the organic stroma, sometimes stand out stained orange. If pyronin is used for the staining the central part of the body usually remains unstained while the peripheral part take on a greyish blue to reddish violet colour. The remaining part of the giant cell containing the Schaumann body usually stains red by this method.

Discussion

As the earlier review of the literature showed, many different views have been put forward concerning the nature of the Schaumann bodies. Most of them, however, seem to be false.

The present author has already pointed out that the Langhans giant cells in this series often show signs of degeneration in the form of a change in the structure and staining properties of the cytoplasm. In his experience there is such a marked correlation between the appearance of this, probably physical (colloid chemical) change in the cytoplasm and the earliest stages in the development of the Schaumann bodies that it seems justifiable to consider these bodies as the result of an advanced degeneration of the giant cells. The prerequisite for their formation seems to be a precipitation of the cell protein with deposition of salts in the precipitate. Thus, in the opinion of the present author, the Schaumann bodies represent autochthonous, intracellular concrements. The fact that they have a concentrically laminated structure similar to that seen in other structures known to be of the nature of concrements supports this suggestion. Thus, where the pathogenesis of the Schaumann bodies is concerned, the present author adheres to the hypothesis put forward by the German authors (e.g. Schüppel, 1871) and referred to previously, namely, that they are the expression of a regressive metamorphosis of the Langhans giant cells. According to this view the presence of the structures in question in the granulomatous lesions must be considered as the result and not the cause of the lesions.

The present author has been unable to discover any reliable evidence supporting the opinion put forward by several authors (e.g. Vogt, 1950) that the organic stroma of the Schaumann bodies is composed of elastic fibrils.

Attention has already been drawn to the fact that Schaumann bodies may sometimes be seen lying free in intact lymphoid tissue, often in groups. On the basis of his hypothesis concerning their pathogenesis the present author considers that these free lying Schaumann bodies represent giant cells which have been completely converted into concrements. This view is supported by the fact that, as already pointed out, Langhans giant cells containing Schaumann bodies are sometimes found in groups outside the tubercles.

It has already been mentioned that Schaumann bodies are seldom reported in classical tuberculosis, while they are often stated to be characteristic or even pathognomonic of l.b. It is thus noteworthy, and perhaps not altogether without significance for the assessment of the etiology of l.b., that they are so commonly to be seen in the form of tuberculosis now under discussion.

Little appears to be known, so far as can be told from the literature, about the characteristic anisotropy shown by the Schaumann bodies. This, in association with ignorance of the fact that they are present, not only in l.b. but also in the form of tuberculosis in question, has led to theories which the present author believes to be incorrect. Refvem's theory that l.b. is a more or less generalised foreign body reaction to a mineral material is one example. There can be no doubt that at least some of the so-called exogenous mineral particles described by him in his work on l.b. are, in fact, Schaumann bodies. The simple fact that these structures are seen in many of the lymph nodes in this series seems enough to refute his theory.

Regressive Changes

Caseous necrosis

Insignificant amounts of caseation are present in the central parts of the tubercles in 12 cases. In these cases and in a few others necrobiotic changes in the epithelioid cells are also present in the centres of the tubercles. In their earlier stages these manifest themselves in the form of diminished staining of the nuclei of the epithelioid cells while in later stages they take the form of chromatolysis and increasing acidophilia of the cytoplasm. In an advanced stage of necrobiosis a low magnification shows the centre of the tubercle occupied by an acidophil substance which often appears to be homogeneous but in which the use of a higher magnification and a suitable stop will reveal definite shadows of cells.

Fibrillar (fibrinoid) necrosis

The regressive change occurring in l.b. which was described by Ricker and Clark (1949) as fibrinoid necrosis, is present in no less than 40 of the 58 cases in this series.

Although this type of necrosis is commonest in the central parts of the tubercles one may often see a change which is similar in its morphology and staining properties occurring in the peripheral parts of two or more tubercles which abut on one another.

As was mentioned by Ricker and Clark, the regions of the tubercles affected by fibrinoid necrosis present a fibrillar structure. In sections which have not been specially stained this fibrillar structure can only be detected when using a high magnification and a small stop. As the course of the fibrils is usually irregular the necrosis in the centres of the tubercles generally looks like an irregular network into which the precollagenous fibres pass directly (Pl. IV A, Fig. 43). The altered fibrils are somewhat coarser than is the precollagenous fibrous network of the tubercles and, in many places they show knotty swellings (Fig. 43). Fragmentation of the fibrils is often seen in the necrotic area.

As Ricker and Clark described in l.b. so, in the present cases, the areas of fibrinoid necrosis are acellular apart from an occasional apparently intact lymphocyte or red corpuscle in the meshes of the network.

The areas of fibrinoid necrosis have special staining properties. In sections stained by the hematoxylin-van Gieson method these areas stand out even at low magnifications by reason of their clear shining yellow or orange colour, unlike the areas of caseation which appear a pale greyish yellow colour. The network stains red with azan (Pl. IV A) and when Mallory's method is used it is yellowish red. In sections which have been stained for fibrin only occasional fibres take on a bluish violet colour. If silver impregnation according to the method of Pap, Snook or Wilder is used, the threads take on a grey or black colour. In preparations stained in this way the transition of the precollagenous fibrils of the tubercle into the fibrillar network of the fibrinoid degenerate foci can be clearly seen as can the knotty structure of the altered fibrils (Fig. 43).

Discussion

It is interesting that the fibrinoid necrosis which is considered by Ricker and Clark to be so characteristic of l.b. is so widespread in the present series of lymph nodes as well. This must surely be of some importance in an assessment of the etiology and pathogenesis of l.b.

It is a question of some significance as to how far this lesion is identical with the classical fibrinoid degeneration and necrosis which is specially common in allergic diseases such as the various manifestations of rheumatic fever. In that context the concept of fibrinoid degeneration and necrosis refers to a change in the collagenous connective tissue in respect to its structure and staining properties (Eickhoff, 1948, and others). In the present context the fact that the change usually takes place in the centre of the tubercles which only contain precollagenous

fibrils makes it clear that it is not the same as the classical fibrinoid degeneration. It is true that the staining properties of the lesion under discussion are similar to those seen in the classical fibrinoid degeneration in so far as silver impregnation and azan staining are concerned but the results of staining for fibrin are not. The present author therefore considers that it is not identical with the classical fibrinoid degeneration. It should, however, be clearly distinguished from caseous necrosis on account of its characteristic morphology and staining properties. The name *fibrillar* necrosis is therefore suggested.

As concerns the pathogenesis of fibrillar necrosis, a thorough study has led the present author to the opinion that the prerequisite for its appearance is the necrobiotic change in the epithelioid cells. As already pointed out, this occurs mostly in the centres of the tubercles and thus, in general, has the same localisation as the fibrillar necrosis. The cellular necrobiosis should probably be considered as being the effect of a relatively mild toxic action of broken down tubercle bacilli on the tissues, and thus, from the point of view of pathogenesis, to be compared with caseous necrosis.

It will be shown later that in this form of tuberculosis the tubercles are traversed by a slender precollagenous network. The necrobiosis leads to the appearance of cellular protein debris and it seems probable that this permeates the precollagenous fibrils, causing them to become coarser and change their staining properties as has already been described. As the necrobiotic change progresses from the centre of the tubercles towards the periphery larger numbers of the precollagenous fibrils are affected. Thus the area affected by the fibrillar necrosis appears to be larger the greater the extent of the necrobiosis.

There are two reasons for supposing that this interpretation of the pathogenesis of the fibrillar necrosis is correct. First there is the circumstance that this necrosis is, as already mentioned, localised in the centres of the tubercles, i.e. just in the place where the necrobiosis is usually most pronounced. In the second place one can see, especially clearly in silver impregnated or azan sections, how the precollagenous fibres lying in contact with the cellular debris at the margin of the area of fibrillar necrosis, become coarser and change their staining properties, showing a continuous transition to the fibrils of the necrotic area (Fig. 43).

Perifocal Inflammatory Reaction

Although it is harder to judge of the degree of perifocal reaction in the lymph nodes than in, for example, the skin, it is clear that the lymphocytic reaction in the marginal areas of the tubercles is very slight indeed. This fact was often mentioned in the reports of the pathologists.

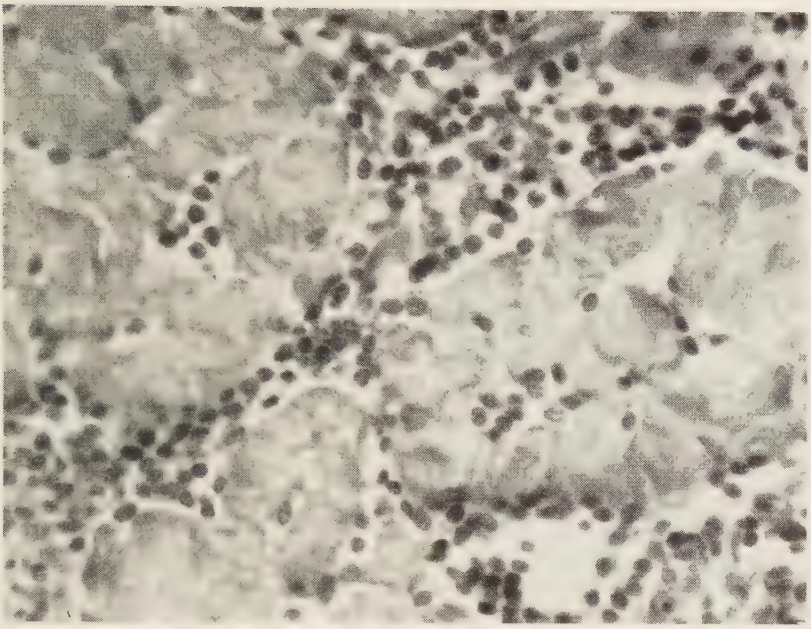


Fig. 14 (Case I: 9). Lymph node with tubercles showing a high degree of fibrohyaline induration. Htx.-v.G.

Indurative Changes

In the great majority of the lymph nodes in this series the tubercles are traversed by a slender precollagenous network. Gradually this network becomes closer and coarser and, as the fibrosis proceeds, the tubercles assume the character of the so-called hard tubercles. The final stage in this process is represented by tubercles which have undergone complete fibrohyaline induration (Fig. 14). In a few of the lymph nodes, however, the reticulum has only developed in a more or less fragmentary way. This may be due to the fact that, in these cases the process is in a relatively early stage. It is particularly common in cases where the individual tubercles have coalesced to form larger conglomerates.

At the same time as the intragranulomatous fibrosis there appears a perigranulomatous hyaline substance in the form of bands or laminae (Fig. 15). In preparations stained by the hematoxylin – v. Gieson method this does not always stain red but sometimes yellow or yellowish red, with azan it stains partly red. In some cases such hyalin is also found around the larger blood vessels, where it may take the form of regular rings (Fig. 16).

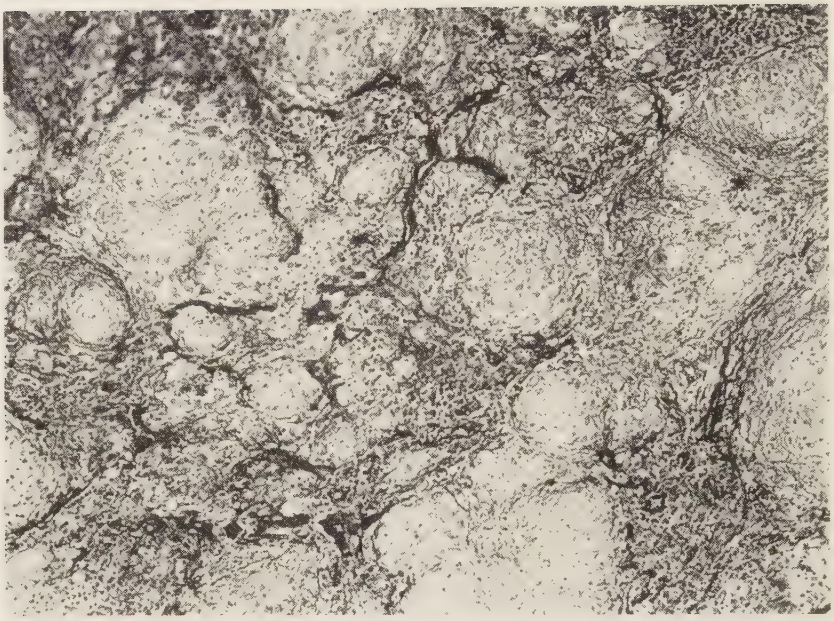


Fig. 15 (Case I: 52). Lymph node with miliary tubercles showing pronounced fibrous induration and marked perigranulomatous hyalinosis. Htx.-v.G.

In most of the cases there is a marked tendency for the precollagenous and collagenous fibres in the periphery to show a concentric orientation. The epithelioid cells are thus also arranged concentrically (Fig. 17).

Discussion

Special interest attaches to the perigranulomatous hyalinosis as it seems to be the same as that which Teilum described in l.b. and which he interpreted as being the morphological expression of an allergic hyperglobulinosis of the reticuloendothelial system caused by chronic stimulation of the antibody forming mechanism of the plasma cells. This theory of Teilum's also seems applicable to the lesions in the form of tuberculosis in question. It is possible that the etiological agent which was demonstrated in this series of nodes, namely the acid-fast rods, might have caused chronic stimulation of the local production of antibodies by means of their breakdown products. It is true that plasma cells are not so common as in series II but the hyalinosis may be a summation effect of the local antibody formation which has been proceeding for a long time with precipitation of antibody protein in the form of hyalin.

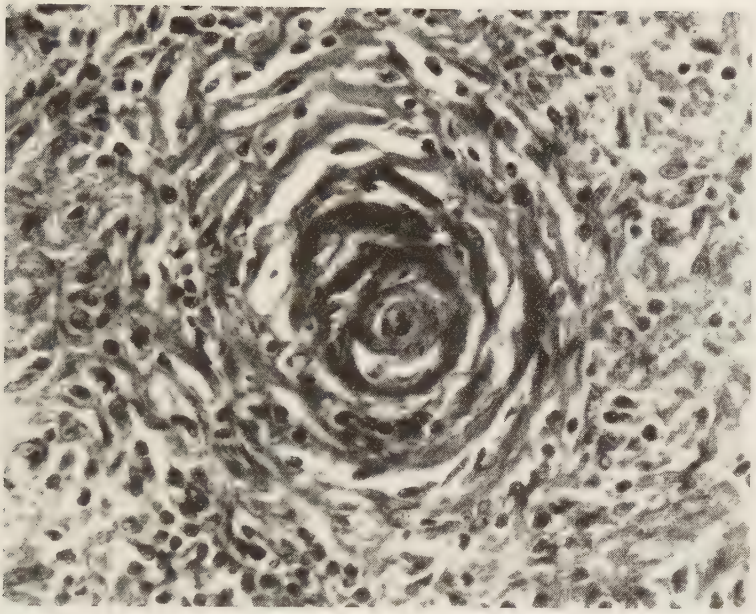


Fig. 16 (Case I: 55). Lymph node with lamellar perivascular hyalinosis. Htx.-v.G.

Vascular Lesions

A characteristic feature of this series of lymph nodes is that the tubercles are largely perivascular in situation .Vessels which have been cut longitudinally sometimes appear to be surrounded by mantles of granuloma tissue (Fig. 18). Such vessels are usually unchanged themselves. Only occasionally they show thrombotic obliteration. In a couple of cases inflammatory lesions were seen in vessels not surrounded by tubercles. In these cases the lesion either looked like a non-specific panarteritis (Fig. 19) or took the form of small epithelioid cell tubercles projecting into the vascular lumen.

Bacterial Findings

In the great majority of the cases acid-fast bacilli were found without great difficulty. In some cases, however, finding them was a very time consuming business. Thus, in one case no less than 18 sections of about 15 × 18 mm were searched before an acid-fast rod was discovered. The demonstration of an acid-fast rod in each of these cases necessitated the careful examination of about 240 preparations altogether. About

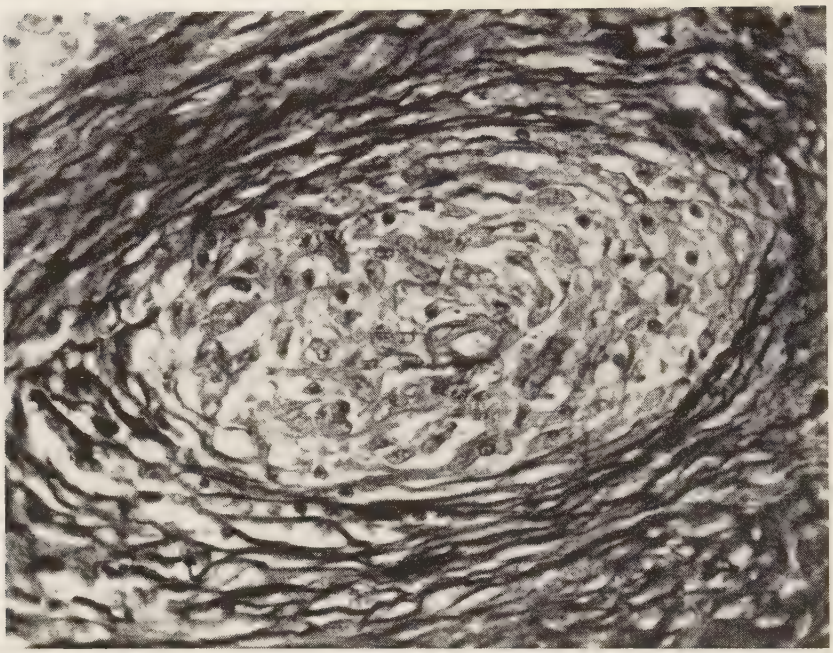


Fig. 17 (Case I: 56). A tubercle showing concentric arrangement of both epithelioid cells and collagenous fibres. Htx.-v.G.

50 per cent of the bacilli found were lying inside giant cells (Figs. 20 and 21).

The bacilli observed had the morphology of tubercle bacilli.

In only one case (57) was the author able to obtain material from a lymph node for culture and guinea pig test. Acid-fast rods grew on Loewenstein's medium and two animals inoculated with finely divided lymph node tissue died two months later of generalised tuberculosis. The tubercle bacilli were of the human type.

Discussion

Some workers have stated that it is common to find tubercle bacilli both in normal human lymph nodes and in those affected by some disease other than tuberculosis. This view is based on a number of observations made shortly after the discovery of the bacillus of Koch. Thus Loomis (1890) was able to isolate tubercle bacilli by animal tests from the bronchial lymph nodes of six out of 15 patients dying of diseases other than tuberculosis. Similar experiences were reported by

Fig. 18 (Case I: 1). A vessel surrounded by a mantle of tuberculous granuloma tissue. Htx.-v.G.

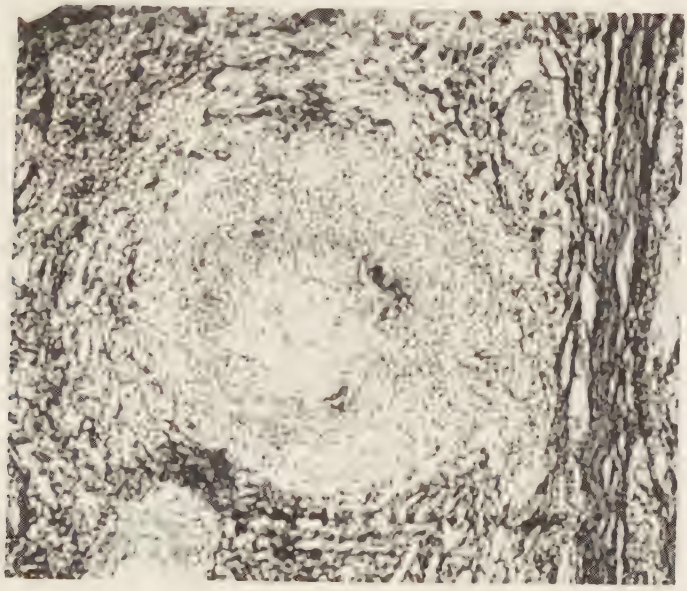


Fig. 19 (Case I: 23). Tuberculous panarteritis in a lymph node. Htx.-v.G.

Pizzini (1892) and Spengler (1893) among others, using lymph nodes showing no macroscopical sign of tuberculosis. As the material used in these investigations was not microscopically examined one cannot be certain that tuberculosis was not present in the cases in which the animal tests were positive. The results of these investigations are, therefore, not convincing evidence that tubercle bacilli are to be found in lymph nodes unaffected by tuberculosis. Nor have more recent investigations lent support to this supposition. Thus Adamson (1949) published a comparative histopathological and bacteriological investigation of a material consisting of 45 tonsils, 444 lymph nodes and 46 spleens, all derived from persons who showed no sign of active tuberculosis. He showed that tubercle bacilli could not be isolated from a single one of these cases. On the other hand, when a series of similar composition but somewhat smaller and derived from patients with active tuberculosis was used, tubercle bacilli and the tissue changes characteristic of tuberculosis were often found.

There is thus no support for the view that tubercle bacilli are present in lymph nodes which are not affected by tuberculous disease. One may, however, wonder whether the same is true of saprophytic mycobacteria, the more so as it is known to be possible to isolate quite a number of strains of mycobacteria of this type from chronic skin lesions, e.g. those of leprosy (Gordon, 1937; Gordon and Hagan, 1938). The present author carried out an investigation on a series of 183 lymph nodes showing no obvious microscopical lesions. At least one, often several, Ziehl-Neelsen stained preparations were studied from each node with a view to demonstrating acid-fast rods. None, however, were found. It would therefore seem that there is no justification for transferring the results obtained on chronic skin lesions to *healthy* lymph nodes.

In regard to *diseased* lymph nodes, however, e.g. those which are the seat of metastatic tumours, it seems possible that acid-fast saprophytes might gain entry and multiply in the destroyed lymphoid tissue. This seems even more probable when one considers the results of the examination of chronic skin lesions mentioned above. According to the experience of the present author such an occurrence must be very rare, if, indeed, it ever happens. Thus, in an investigation of nine lymph nodes which were the seat of widespread and largely necrotic cancerous lesions the author was unable to demonstrate acid-fast bacilli in a single one of the 180 Ziehl-Neelsen stained sections.

It therefore seems that the acid-fast rods seen in the sections must be regarded as the cause of the lesions in this series of lymph nodes. This suggestion is supported by a fact already mentioned, namely that a large number of these bacilli were found lying in the giant cells, which would probably not have been the case if they had been merely harmless saprophytes.

The next question is whether the bacilli which were demonstrated

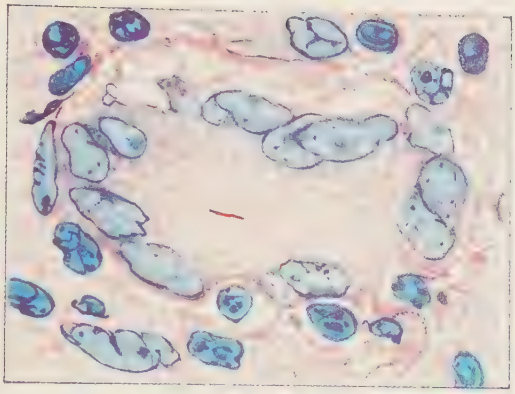


Fig. 20 (Case I: 18). Acid-fast rod in a giant cell. × 1000. Ziehl-Neelsen.

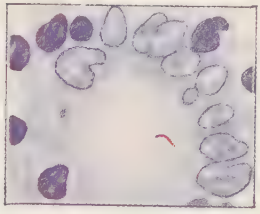
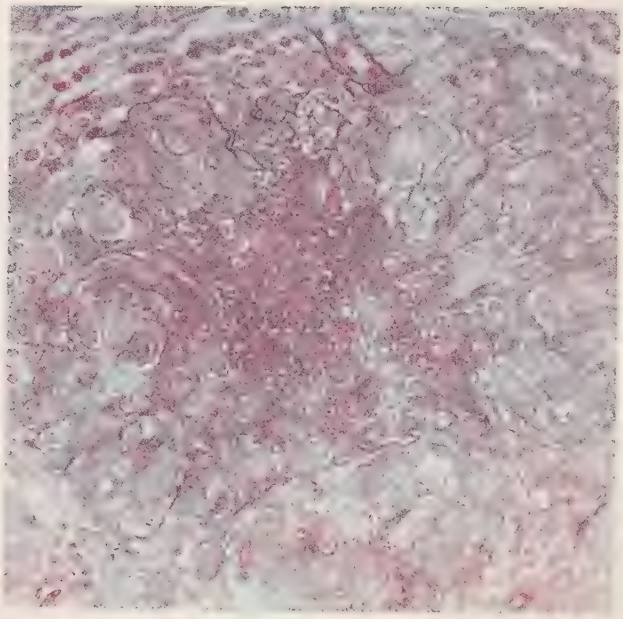
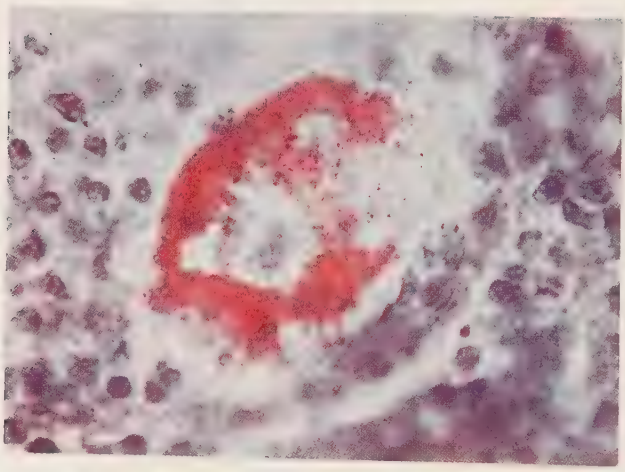


Fig. 21 (Case I: 28). Acid-fast rod in a giant cell. × 1000. Ziehl-Neelsen.



A. (Case I: 26.) Tubercle with central fibrillar necrosis. Azan.



B. (Case II: 40.) Fat stained preparation showing a giant cell with an asteroid body and strongly sudanophil granulation of the cytoplasm.

really were tubercle bacilli. As has already been pointed out, the enlarged lymph nodes had not given the clinicians the impression of being tuberculous. Neither did the active changes in the lungs and hilar regions which were associated with the enlargement of the peripheral nodes in seven cases resemble a manifestation of classical tuberculosis. Clinical analysis of the material, however, has led to observations which suggest, to some extent, that the enlargement of the lymph nodes is tuberculous. Thus a family history of tuberculosis was frequently elicited and in several of the cases there were found residual effects of earlier tuberculous infection in the form of calcification in the lungs and hilar lymph nodes. Furthermore, the enlargement of the lymph node which led to the inclusion of the patient in the present study was, in some cases, the sequel to a previous tuberculous adenitis of the ordinary type.

There is nothing, from the histological point of view, to suggest that the condition of the lymph nodes under discussion is not tuberculous.

The definite proof that the bacilli found in the lymph nodes really are tubercle bacilli is provided by the positive result of the guinea pig test in one of the cases.

In comparison with the common form of tuberculous lymphadenitis the affection of the lymph nodes here described is atypical in regard to its clinical course as well as its microscopical picture.

In the ordinary form of tuberculous lymphadenitis the swelling of the nodes characteristically proceeds rapidly and is usually associated with fever especially in children. It is sometimes followed by erythema nodosum. The patient often complains of spontaneous pain and tenderness. The later course is characterised by the tendency to liquefaction and fistula formation. In favourable cases a gradual regression sets in which is, however, often interrupted by exacerbations. Gradually, often after several years, the tendency to heal becomes pronounced. The fistulae may granulate together, the remaining caseous necrosis may become inspissated and calcified and, as a sign of the tuberculous lymphadenitis, there may remain a scarred retraction of the skin or calcified nodes in the form of hard lumps of irregular contour.

The case histories describing the origin and development of the enlargement of the lymph nodes in the cases here reported, however, tell quite a different story. As has been stated, the enlargement of the nodes appeared gradually. Pain only occurred exceptionally and then in association with infection of the upper respiratory tract. Similarly, reddening of the overlying skin was never observed and the enlarged node was usually freely mobile with respect to both the skin and the underlying tissues. The consistency was given as firm and elastic or hard. The reason why the patient consulted a physician for the relatively slight trouble caused by the disease was often a fear that the swelling might be malignant or sometimes the opinion that it was unsightly.

The atypical clinical course in comparison with that of classical

tuberculous lymphadenitis combined with the appearance of the specimens removed at operation has, as was stated before, often given clinicians a false idea as to the nature of the lesion.

It has already been mentioned that the microscopical picture also differs significantly from that which is characteristic of classical tuberculosis. Thus the lesion usually respects the boundary formed by the capsule of the lymph node.

The individual tubercles only coalesce to an insignificant extent. Regressive changes in the form of caseous necrosis are practically absent while the tendency of the tubercles to heal by fibrohyaline induration is often pronounced. Finally, the picture is characterised by the common presence of Schaumann bodies.

Several circumstances contradict the view that in these cases we are dealing with relatively early stages of a process which, given time to develop, would take on the character of classical tuberculous lymphadenitis. For example, these enlarged nodes have often lasted for a long time, in many cases for several years, without the onset of periadenitis, liquefaction or fistula formation. Further, in cases where there were multiple enlarged lymph nodes, those which were not excised did not later take on the characteristics of classical tuberculous lymphadenitis. Finally, in most cases there are histological signs of healing in the form of fibrous induration.

It is a remarkable fact that bacilli should still be found in the tubercles in spite of the long duration of the enlargement of the lymph nodes. As the patient does not usually present an active tuberculous focus in the lungs for example, from which bacilli might be continually transferred to the lymph nodes, it must be assumed that those which were seen in the nodes were the descendants of those which first infected it. As the condition of the lymph nodes often remained stationary over a period of years the bacilli which were seen in them must be supposed to be bacilli of low virulence but ones which the defensive resources of the organism was, nevertheless, unable to destroy. The situation between the parasite and host may be characterised as a constant struggle in which the host has the upper hand but cannot defeat the invader. If we assume that the lifetime of the individual bacillus is not particularly long but that there is a continual destruction of microorganisms in the node, this should lead to strong specific immunisation of the organism.

It would appear, however, from certain observations, that the patients had a relatively high immunity to tuberculosis even at the time when the nodes first began to swell. Of interest in this connection is a case in which the form of tuberculosis in question and the classical form of tuberculosis were both present in the same lymph node (Fig. 22). In all probability the small caseous focus which may be seen in one of the lymph nodes in the picture dates from earlier than the dominating

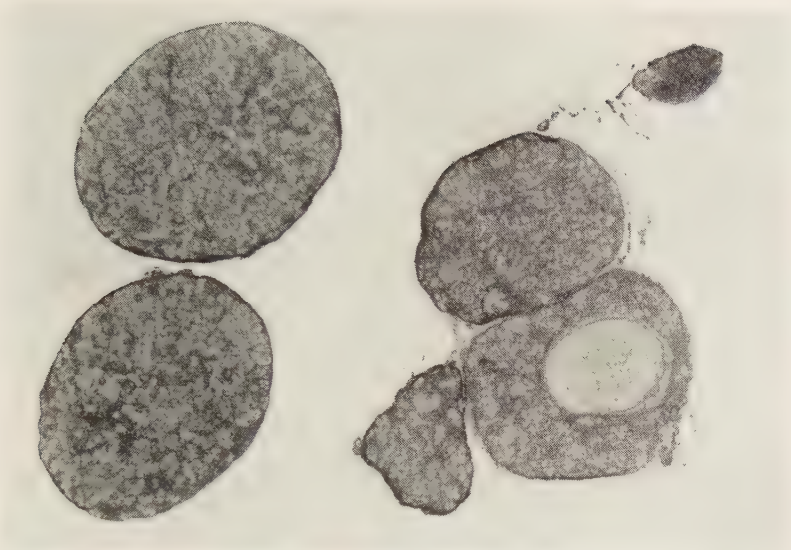


Fig. 22 (U. 7292/52). ♂, born 1902. No family history of tuberculosis. At the age of 24 the patient was operated on for tuberculous nodes of the left side of the neck. Since the age of 25 enlarged nodes in the right side of the neck. Gradually they increased in size and several new ones appeared in the right supraclavicular fossa. In 1952 the nodes were extirpated. They show the pattern characteristic of series I. In one of them there is also a caseous focus probably older than the miliary scattering. Acid-fast rods +. Htx.-v.G.

miliary scattering of tubercles which probably arose as a result of an increase in the immunity.

It is an interesting fact that in some of these cases there is obviously a good immunity to tuberculosis associated with a low sensitivity to tuberculin. Several authors (Rich and McCordock, 1929; Rich, 1951, and others) have, however, stated that a high degree of immunity may exist in the absence of allergy.

The fact that the affected lymph nodes are usually situated in the neck might be expected to provide an indication of the pathogenesis of the condition. It has, in fact, long been thought that tuberculous affection of the nodes of the neck was usually part of a primary complex in which the primary focus was in the throat, e.g. in the tonsils, or the upper part of the alimentary tract. It is hardly surprising that in the cases presenting adenitis of the neck the route of infection should often be alimentary (infected milk). The opinion that tuberculous infection of the nodes of the neck is usually part of a primary complex is supported by the fact that in epidemics of alimentary infection with tuberculosis such as have been described in Sweden and other countries.

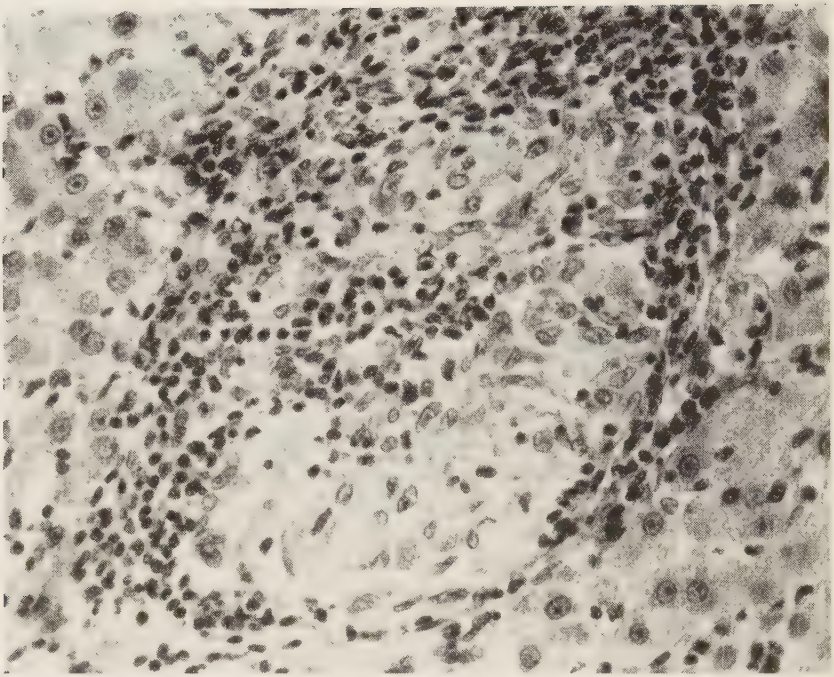


Fig. 23 (U. 289/53). ♂, born 1911. Abdominal pain of long duration culminating in the spring 1952. Associated with icterus. Liver tests showed signs of hepatitis. Joint pains in autumn 1952. Jan. 1953 operation: Exploratory laparotomy. The liver was found to be rather hard with an irregular granular surface. Biopsy. *Microscopic examination* (Prof. Gellerstedt): Cirrhotic form of granulomatous inflammation somewhat reminiscent of the lesions seen in 1.b. The picture shows a tubercle situated in the portal connective tissue which is infiltrated with lymphocytes. No caseation. Acid-fast rods +. The patient also had enlarged nodes in the neck and axillae. Extirpation of a node from the neck. *Patho-anatomical diagnosis:* Tuberculosis. Acid-fast rods +. Electrophoretic determination of the serum proteins: Total protein 9.4 %, albumin 3.42 %, globulin 5.92 % of which γ-globulin 4.15 %.

affection of the nodes of the neck dominated the clinical picture. In an epidemic of this kind in a south-west Swedish community described by Ståhl (1939) there was tuberculous lymphadenitis of the neck in half the cases, while in an epidemic of bovine tuberculosis described by Törnell (1938) among the female textile workers in a Swedish town all patients had infected nodes in the neck. Finally, the well-known tragedy at Lübeck may be recalled, in which the vaccine of Calmette was exchanged for a suspension of virulent bovine tubercle bacilli which was given to the children by mouth. Tuberculous lymphadenitis of the neck occurred in 80 per cent of the children.

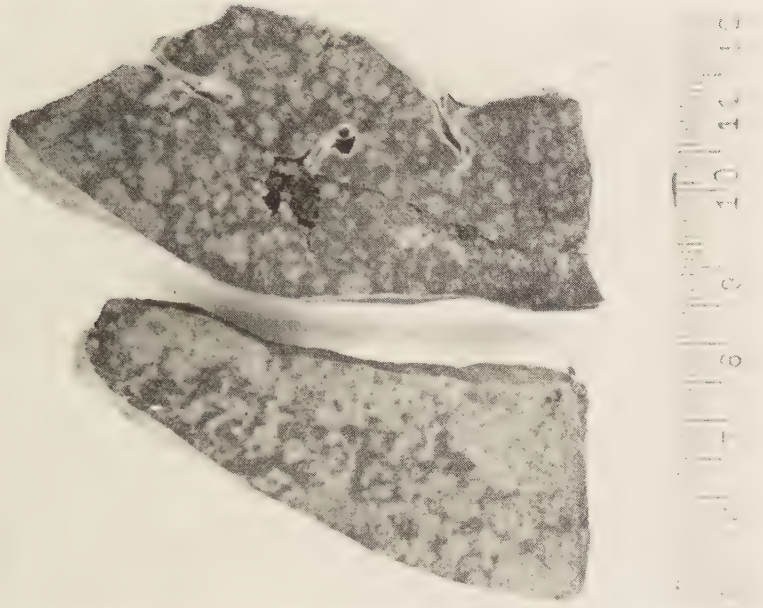


Fig. 24 (Autopsy U. 60/48). ♂, born 1912. Diabetes mellitus since 1928. Diabetic nephropathy and splenomegaly set in gradually. At autopsy the spleen was found to weigh 500 g and several enlarged lymph nodes were found in its hilus. The picture shows large numbers of tubercles in the spleen with no signs of caseation. The pattern is the same as in the lymph nodes of series I. Acid-fast rods could not be demonstrated in sections but a guinea pig test using splenic tissue gave positive result.

It seems, however, extremely unlikely that the enlarged lymph nodes in the neck in the cases under discussion represent a part of a primary complex situated in the upper part of the alimentary tract. As has already been pointed out, the character of the lesions is not destructive like the adenitis associated with a primary complex. Furthermore, some of the patients showed residual signs of a pulmonary primary complex. This brings up the question whether the enlargement of the lymph nodes of the neck is due to endogenous superinfection of those regions (e.g. the tonsils) which are drained by these nodes. This does not seem likely either. Tuberculous lymphadenitis of the neck in persons with open pulmonary tuberculosis is a rare phenomenon. Thus, Wallgren, (1944) made a careful search in 516 such cases but was only able to demonstrate tuberculous lymphadenitis of the neck secondary to the pulmonary tuberculosis in seven of them. However, as a microscopic examination of the enlarged nodes was not carried out, there is, as Wallgren said, no proof that the affection of the lymph nodes was tuberculous even in these cases.

The fact that some of the patients showed residual changes after tuberculous infection of the hilar lymph nodes, associated with the fact that in no less that seven cases the peripheral lymphadenitis was associated with an active and definitely tuberculous process in the hilar regions provides strong support for the view that the lungs are the portal of entry for the infection and that the lesions of the peripheral lymph nodes are a sequel of atypical primary tuberculosis in the hilar nodes.

It may now be asked whether the peripheral lymphadenitis arises by lymphogenous or hematogenous spread of the tubercle bacilli from the hilar regions. The fact that in some cases paratracheal lymphadenitis could be demonstrated radiographically and the circumstance that the occurrence of lymphadenitis is, in by far the greater number of cases, limited to the neck from the supra-clavicular fossae up to the mandible combine to support the idea that lymphogenous spread plays a dominating part. On the other hand, in the few cases in which the enlargement of the nodes is generalised or is confined to one axilla or one groin, one is probably dealing with hematogenous spread. The intimate topographical relationship between the mediastinal lymph nodes and both the pulmonary vessels and the thoracic duct must borne in mind in this connection.

It is a question of some importance whether or not the form of tuberculosis at present under discussion is identical with the large-celled hyperplasia of the lymph nodes described by Ziegler. Even though his is a summary description and his view that the condition is of a tuberculous nature is ill-founded, there can be little doubt but that they are identical. The name given by Ziegler is, however, somewhat unfortunate. This form of tuberculosis is not confined to the lymph nodes although it occurs most commonly in them; it is also found in other organs such as the liver (Fig. 23), and spleen (Fig. 24), and, as has already been mentioned in the Fallopian tubes (Figs. 11 and 12). Furthermore, the meaning of the term large-celled may not be quite clear, especially to the clinician. The present author therefore proposes the term *chronic hyperplastic tuberculosis* for this form of tuberculosis. The question as to the relation between it and l.b. will be taken up in Chapter 10.

CHAPTER 9

Series II

Lymph Nodes Without Bacilli. Lymphogranulomatosis Benigna

(*Case Reports see pp. 150—174*

Age and Sex Distribution

As was stated earlier, the 58 cases in series I consisted of 30 women and 28 men. The present series consists of 24 men and 26 women.

The youngest patient was 16 and the oldest 70 years old. The age distribution is as follows:

10–19 years	1 case	50–59 years	10 cases
20–29 »	12 cases	60–69 »	4 »
30–39 »	14 »	70–79 »	1 case
40–49 »	8 »		

Apart from the small number of cases in the lowest age group the age distribution is thus much the same as in series I. In both series there are most cases in the age group 30–39 years.

Clinical Picture

The present series differs from the previous one in presenting a greater variety of clinical features and by more widespread affection of the lymph nodes.

In seven cases (4, 29, 35, 38 42, 48, and 50) the illness started with erythema nodosum. In some cases this was associated with joint pains. In three of them there was a recurrence of the erythema (38, 42, and 50). Erythema induratum also appeared in one case (13).

In 43 of the 49 patients whose lungs were examined radiographically there were changes characteristic of l.b. in the form of bilateral hilar enlargement, either alone (Fig. 25) or combined with bilateral changes

in the parenchyma (Fig. 28). In three of these 43 cases (29, 35, and 49) the hilar adenitis was originally seen to be unilateral. In three cases also (19, 22, and 32) no pulmonary changes could be found at the time when the lymph nodes were removed. This may be because the disease had already passed through its pulmonary phase, or because there were never any pulmonary changes.

In three cases the pulmonary lesions must be considered as somewhat atypical of l.b. In case 8 there was a fine speckling of both apices as well as increased opacity in the hilar regions. In case 16 the pulmonary condition was ushered in by a "patch" on one lung. On examination two years later cloudy opacities were seen in the base of one lung field and in the upper part of the other. Finally, in case 40, there was a well-defined infiltration of the parenchyma about the size of a plum below and behind one hilus as well as the bilateral hilar enlargement.

Continuous radiographic checking supported the view that the hilar enlargement in l.b. is primary to the parenchymatous changes and that the occurrence of the latter is usually intimately related to the development of the hilar adenitis. It seems that, occasionally, the parenchymatous changes never develop. Case 13 is an example. Here there was massive hilar enlargement (Fig. 25) which did not show signs of regression till after seven years. No parenchymatous changes in the lungs were observed in spite of frequently repeated radiography.

The radiographic studies have also shown that regression of the pulmonary changes is not associated with calcification, especially in the hilar regions.

Pleurisy occurred in five cases (5, 8, 15, 20, and 23) during the course of the disease. In only one case (23), however, did it dominate the clinical picture. All of these patients were tuberculin negative at the time when the pleurisy appeared.

General enlargement of the peripheral lymph nodes was seen in 16 cases. The enlargement of the nodes was, in general, somewhat less than that in series I. This is probably the reason why the patients had relatively seldom noticed the enlargement themselves and could therefore only give definite information as to its duration in exceptional cases.

There is no noteworthy difference between series I and this series in respect of the consistency of the nodes or of their relationship to one another or to the surrounding tissues. Thus they were firm, not painful or tender and freely moveable in regard to one another and to the surrounding tissues. There was no liquefaction or fistula formation. As in series I the lymph nodes had a firm consistency and showed a greyish yellow and often markedly granular cut surface without the least sign of necrosis.

In comparison with the pulmonary changes and the enlargement of the lymph nodes other symptoms of l.b. were rare. There was pericarditis in one case (8), splenomegaly in four (2, 3, 9, and 22) and in three cases (9, 15, and 27) an apparently benign nephropathy only mani-

Fig. 25 (Case II: 13). Large bilateral hilar lymphomata.

Fig. 26 (Case II: 21). Bilateral enlargement of the hili without sharply defined contours of lymph nodes and with perihilar mottling on both sides. Photograph taken at a time when the patient showed signs of miliary tuberculosis.

lymph nodes were seen in a couple of patients in whom no pulmonary changes could be demonstrated in spite of repeated radiography suggests, however, that the alimentary tract may sometimes be the portal of entry for the infection. The question whether or not the clinical signs of hepatitis present in both these cases were due to l.b. cannot be answered with certainty. Granuloma tissue characteristic of the disease was, however, demonstrated in the liver in one of these two cases.

Judging by the symptoms it would appear that the spread of the infective agent in l.b. is mainly lymphogenous from the probable site of primary infection in the hilar lymph nodes to the other mediastinal nodes and to the nodes of the neck. It is of interest in this connection that Löfgren (1953) observed that paratracheal lymphomata are seen practically only on the right side. The "peripheral" manifestations of the disease, e.g. changes in the eyes, skin and bones, on the other hand, are probably the result of hematogenous spreading of the infective agent. The intimate topographical relationship between the mediastinal nodes and both the pulmonary vessels and the thoracic duct very likely play a part in this spread.

Clinical Relationship to Classical Tuberculosis

While 25.6 per cent of the patients in series I had a family history of tuberculosis, only four of the 45 patients in the present series from whom the necessary information could be obtained had such a history (8.9 per cent). In series I 19.0 per cent of the patients had a previous history of manifest tuberculosis, while such a history was only forthcoming in one case (2 per cent) in the present series. In series I signs of previous tuberculous infection in the form of calcified foci were found in 21.1 per cent while in the present series a pulmonary focus of calcification was only found in one of the 49 patients submitted to pulmonary radiography.

Three of the four patients who had a tuberculous family history were found to be tuberculin positive. The percentage of tuberculin reactors among those who had no such family history was 19.4 per cent.

As already pointed out, the follow up study in series I showed that, of the 31 patients traced, only one (3.3 per cent) had developed tuberculosis and none had died of it in the period between the removal of the lymph node and the follow up. In the present series, on the other hand, at least four (11.1 per cent) of the 36 patients traced had acquired classical pulmonary tuberculosis in the course of a period of similar length. In these four cases the tuberculous complication was pulmonary tuberculosis and tuberculous spondylitis (case 5), pulmonary tuberculosis (case 7), acute miliary tuberculosis (case 21), and tuberculous lymphadenitis (case 28). Furthermore, acid-fast rods (tubercle bacilli?)

were found in the sputum in case 43. Apart from case 21, where the patient is apparently in good health after five years of observation, all these patients have died either of tuberculosis (cases 5 and 7), l.b. and ordinary tuberculosis (case 28) and l.b. (case 43). Four other patients included in this series have also died. In case 2 the cause of death was given as chronic pneumonia and hemorrhagic pericarditis (T.b.?), in case 3 as l.b., in case 18 as carcinoma + heart failure and in case 37 as chronic rheumatic endocarditis. Case 33 was an autopsy case without any clinical background and is therefore not relevant in this connection.

It is worth noting that in the cases in which the early development of classical tuberculosis could be followed the radiographic pulmonary changes remained typical of l.b. only. Thus, in case 21, miliary tuberculosis developed parallel with pulmonary changes characteristic of l.b. (Fig. 26) and manifested itself in the peripheral nodes previously affected by l.b. Further, in case 5, the appearance of tubercle bacilli in the sputum was not associated with the appearance of any new pulmonary changes atypical of l.b.

Discussion

The low percentage of cases with a family history of tuberculosis, 8.9, is worthy of note. It is nearly the same as the percentage Törnell (1954) found in 400 cases giving negative results on screening of the lungs—9.2. Löfgren and Lundbäck (1952), however, found a considerably higher incidence, about 16 per cent, of patients with a family history of tuberculosis in their series of primary pulmonary l.b. This figure is very like that given by Törnell (1954) for a series of 400 persons showing signs of healed tuberculosis, i.e. 15.7.

Another interesting feature in the present series is the almost complete absence of pulmonary calcification indicating previous tuberculous infection. According to the forementioned investigation of Löfgren and Lundbäck it is only the cases most typical of l.b. in respect to their sensitivity to tuberculin, i.e. the tuberculin negative ones, which practically lack pulmonary calcifications. Thus, these were present in only 2 per cent of their tuberculin negative series but in no less than about 20 per cent of their tuberculin positive series. This is remarkable, considering that the incidence of a family history of tuberculosis was the same in both series of these authors. It is equally remarkable that 9.8 per cent of the patients in their tuberculin positive series had had manifest classical tuberculosis before they became ill with l.b., yet not a single patient in their tuberculin negative series. This, in fact, means that the deleterious effect of a family history of tuberculosis has been practically eliminated in the tuberculin negative series, a fact which should be borne in mind when considering the etiology and pathogenesis of l.b.

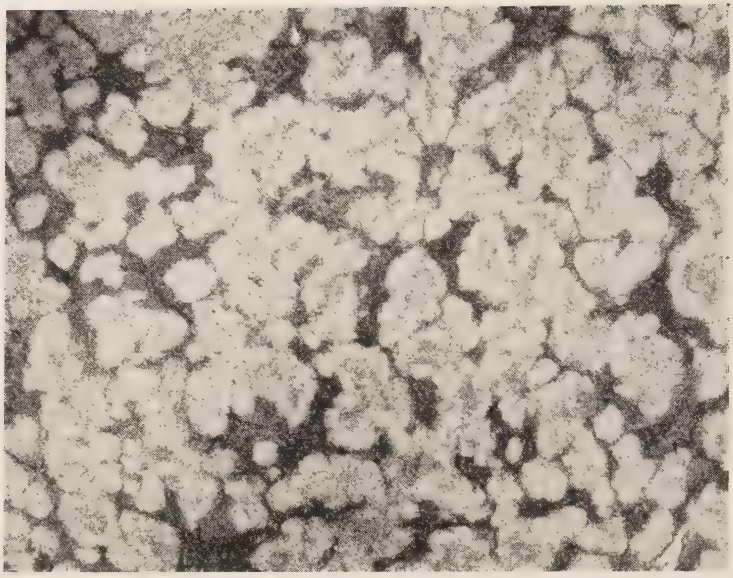


Fig. 31 (Case II: 19). Lymph node with miliary granulomata arranged in groups and with only a slight tendency to coalesce. Htx.-v.G.

Microscopical Picture of the Lymphadenitis

General Pattern

The great majority of the lymph nodes in this series show a diffuse and, generally, extremely dense scattering of submiliary-miliary epithelioid cell foci (Fig. 30). The lesion in these cases is extremely monotonous and easily distinguished from the one in series I showing a rosette or trefoil-like pattern. Even in the present series, however, there are a few cases in which the granulomata are arranged in groups (Fig. 31). This, combined with the fact that in both this series and series I there are nodes in which the submiliary tubercles are diffusely but sparsely scattered (Fig. 32), means that it is sometimes difficult to distinguish the lymphadenitis of l.b. from that of chronic hyperplastic tuberculosis simply on the basis of the general pattern.

The tubercles in this series have, in general, an even less tendency to coalesce than in series I. The boundaries of the individual granulomata remain distinctly outlined even in nodes in which they are closely packed (Figs. 30, 33, and 45).

The granulomatous process does not affect the capsules and surroundings of the lymph nodes in this series any more than in series I.

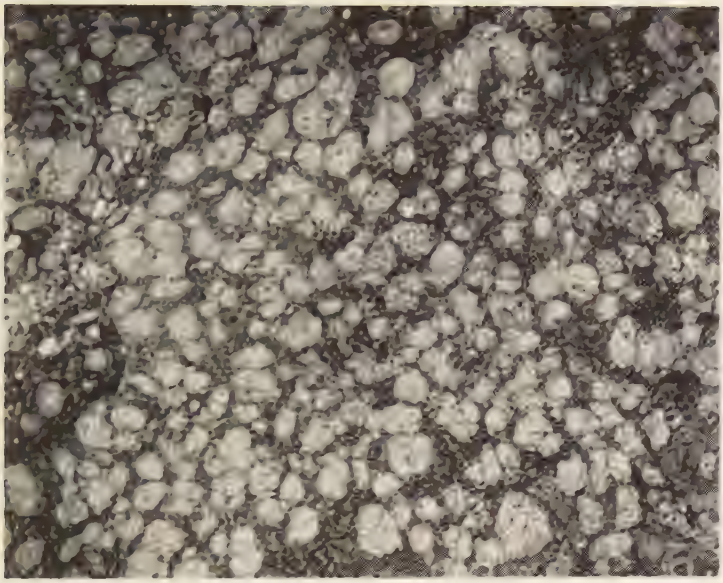


Fig. 32 (Case II: 1). Lymph node with a relatively sparse scattering of submiliary granulomata. Htx.-v.G.

Fig. 33 (Case II: 26). Granulomata lying close together but completely separated from one another, composed almost entirely of epithelioid cells. No caseation. Same node as in Fig. 30. Htx.-v.G.

The Epithelioid Cells

The epithelioid cells have the same general appearance as those in series I. In by far the greater number of the nodes the enlargement of the microcentrum is impressive. While mitotic figures were rare in series I they are relatively common in the present series, especially in the nodes which, judging from the slightness of the indurative changes, the lesions are of fairly recent origin.

As in series I, the epithelioid cells in some of the lymph nodes show alterations in the staining properties of their cytoplasm. Thus, the part of these cells which is not occupied by the enlarged centrosphere is often red in azan stained preparations. Sometimes the staining properties of the whole of the cytoplasm are altered.

Many of the granulomata are characterised by the concentric arrangement of the epithelioid cells, especially in the periphery of them. As in series I, this tendency to a concentric arrangement of the epithelioid cells is most marked in nodes in which the intragranulomatous sclerosis has proceeded furthest.

The Giant Cells

In this series, as in the previous one, the giant cells are usually few in number. In some of the nodes, however, they are numerous, showing that the diagnosis of l.b. is not incompatible with the presence of large numbers of giant cells as some authors stated.

The morphology of the giant cells is the same in every respect as in series I. As in classical tuberculosis they show great variety in both size and shape. There are giant cells which may be considered as of normal size and also some which look shrunken and, in some lymph nodes, others which are even larger than usual and contain an unusually large number of nuclei. As in series I, it is these cells, reminiscent of foreign body giant cells, which most often contain inclusion bodies (Fig. 36).

Enlargement of the microcentra of the giant cells occurs to about the same extent in this series as in series I (Fig. 34). The staining properties of their cytoplasm are also sometimes altered in the same way as those of the epithelioid cells.

Discussion

The alterations in the staining properties of the cytoplasm of both the epithelioid and giant cells may well be supposed to be due to a change in the colloidal system of the cellular protein. The question as to whether this change is associated with the hyperglobulinosis in the reticuloendothelial system which Teilum (1948) considers to be present in l.b. is hard to answer. However, it does not seem unlikely.

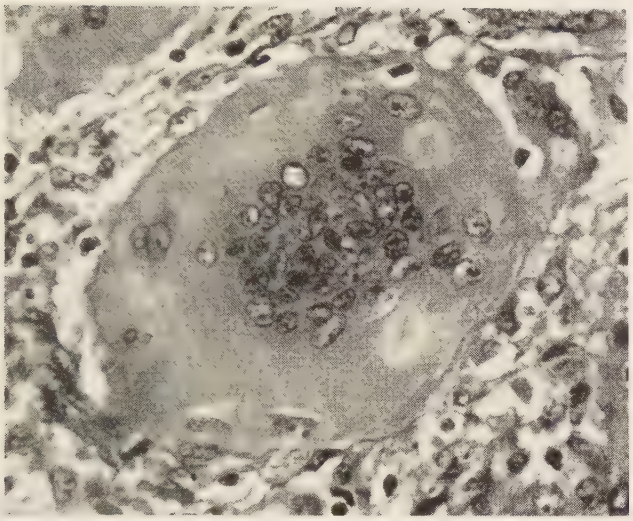


Fig. 34 (Case II: 40). Giant cell with two enlarged microcentra. Htx.-v.G.

The Inclusion Bodies

While Schaumann bodies were seen in 22.4 per cent of the cases in series I they were only seen in five cases (5, 11, 13, 21, and 28) in this series (10 per cent). The type of inclusion body most typical of this series is, however, the asteriod body. These were found in no less than 14 of the cases (28 per cent). As already stated, this type of inclusion body was only found in 5.2 per cent in series I.

THE SCHAUMANN BODY

The Schaumann bodies in this series have the same morphology as those in series I.

As this type of inclusion body is more typical of the chronic hyperplastic tuberculosis than of the present series it is a matter of some interest to ascertain whether there are any similarities between the five cases in which Schaumann bodies were found and the cases in series I. There seems to be only one relevant likeness. In four of them there is a clinical relation to classical tuberculosis. Thus, in case 5 a nephew of the patient had pulmonary tuberculosis and tubercle bacilli were found in her own sputum. In addition this patient later acquired tuberculous spondylitis. In case 13 the patient's 4 year old daughter had tuberculosis and he himself acquired erythema induratum during the course of his illness. In case 21 miliary tuberculosis developed, closely related in time to l.b. Finally, in case 28 both the husband and the son of the patient

had pulmonary tuberculosis. The patient herself had also had tuberculosis before the onset of the l.b. and developed it also in the terminal stages of her illness.

Discussion

The fact that, of the five cases in which Schaumann bodies were found, four were so closely associated with classical tuberculosis, emphasises two questions. The first is whether it was a coincidence that the cases in which the Schaumann bodies were seen in the lymph nodes were so closely related to classical tuberculosis. In 45 of the 50 cases in the present series it was possible to obtain information as to the occurrence of tuberculosis in the immediate surroundings of the patient. In eight of these cases tuberculosis was present in the environment of the patient. As Schaumann bodies were present in the lymph nodes in four of these cases and in only one of the 37 cases in which no close contact with tuberculosis could be discovered, it is hard to believe that the combination of Schaumann bodies in the lymph nodes and tuberculosis in the environment of these patients is purely fortuitous. It is even harder to maintain this position in view of the fact that, as has already been pointed out, classical tuberculosis developed during the course of the illness of four of the five patients with Schaumann bodies while there was only one suspected case of classical tuberculosis among the cases without these bodies.

The other question is whether the cases in which Schaumann bodies were seen in the lymph nodes really were cases of l.b. at all. In view of the fact that these inclusions are, as has already been pointed out, more characteristic of the chronic hyperplastic type of tuberculosis than of l.b., it may be wondered whether the five nodes in which the Schaumann bodies were found came, not from cases of l.b. but from cases of chronic hyperplastic tuberculosis. It could also be suggested that in these cases there was a double infection with l.b., in the sense of a disease *per se*, and with chronic hyperplastic tuberculosis which only manifested itself in the form of adenitis. Such a hypothesis, if correct, would lead, among other things, to a great simplification of the microscopical differentiation between the two diseases. It would mean that enlarged lymph nodes with a tuberculoid structure could be attributed to chronic hyperplastic tuberculosis if there were Schaumann bodies in the giant cells. Is it possible to simplify the problem to this extent? If one looks at case 5 one will see that the clinical picture is composed of pulmonary changes, exudative pleurisy, enlargement of the lymph nodes in the axillae and groins, skeletal lesions, negative tuberculin reaction and monocytosis. There can be no doubt that this symptom complex is characteristic of l.b. The microscopic picture is also characteristic and in 29 sections no acid-fast rods could be found. In case 11 both the clinical and the

microscopical pictures are typical of l.b. In case 13 the clinical picture includes bilateral hilar enlargement which remained stationary over several years. The lesion in the lymph node is characteristic of l.b. and no acid-fast rods were found in the 13 sections. In case 21 the account of the symptomatology is certainly meagre but enlargement of the lymph nodes of the groins in association with a negative tuberculin test gives good ground for a clinical diagnosis of l.b. Also, the microscopic picture was typical. In 80 tissue sections no acid-fast rods could be found. In case 28 the diagnosis of l.b. is supported by the presence of bilateral hilar enlargement associated with a negative tuberculin reaction and hyperglobulinemia. The microscopic picture of two lymph nodes removed on different occasions was also typical of l.b.

Briefly, it may be said of these five cases, that both the clinical and microscopical pictures point to l.b. and not to the chronic hyperplastic form of tuberculosis.

There remains the question as to whether there might not be a double etiology in these five cases, the chronic hyperplastic tuberculosis causing the enlargement of the lymph nodes while the l.b. caused the rest of the symptoms. It must be pointed out that it is most improbable that such a combination should occur in 10 per cent of the cases. Furthermore, the lesions in the lymph node do not agree with this hyperplastic form of tuberculosis and, as has already been pointed out, no acid-fast rods could be found in spite of a diligent search. It may thus be taken that there cannot have been a double etiology in these five cases. The changes in the lymph nodes must therefore be considered as having been caused by l.b. and Schaumann bodies as distinctive features of both l.b. and chronic hyperplastic tuberculosis.

As this type of inclusion has been considered to be particularly characteristic of l.b. and even to be a guide in the microscopic differentiation between l.b. and tuberculosis it is remarkable that they are so rare in this series compared to the previous one. The reason for this may be that cases of chronic hyperplastic tuberculosis have hitherto been wrongly diagnosed to some extent as l.b., but it may also be explained by the fact that the series of l.b. in the present investigation is mainly comprised of chronical, tuberculin negative cases.

The asteroid body

As already stated, asteroid bodies are present in 14 (28 per cent) of the cases in this series. In most of them they are plentiful. In the study of the morphological and staining characteristics of these inclusions use has also been made of the case of salpingitis already described.

It is most usual to find only one asteroid, though two or three may be found in one giant cell. In the case of the smaller giant cells the inclusion usually lies in the middle (Fig. 35). In the larger cells they

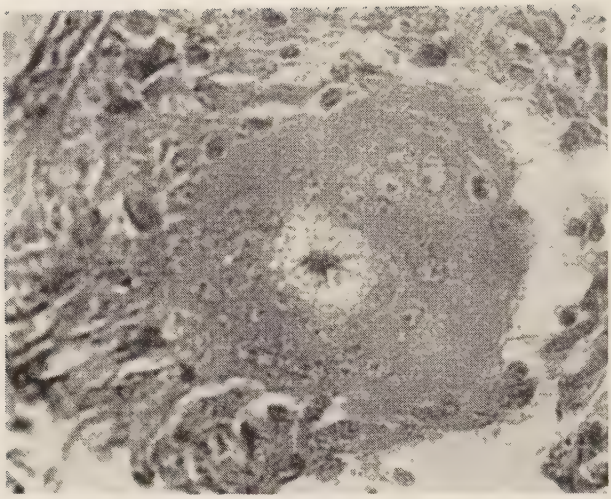


Fig. 35 (Case II: 10). Giant cell with an asteroid body in the early stage of development. Ziehl-Neelsen.

usually lie peripherally, though in general they do not encroach on the outermost part of the giant cell (Fig. 36).

The diameter of the asteroids is usually about 30 μ but may be up to 50 μ—60 μ. In their centres there are one or more rounded, solid, granular structures from which the rays emanate. These are, as a rule, broader in their central than in their peripheral parts, which are often bowed so that the whole formation may be compared to the frame of an umbrella (Fig. 36). Some asteroids have fine slender rays (Figs. 35 and 36) while others have broad leaf-shaped ones (Fig. 37).

While some of the peripheral asteroids lie in apparently intact cytoplasm (Fig. 36) others lie in larger or smaller spaces composed of vacuoles the walls of which are formed by narrow bridges of cytoplasm (Figs. 37 and 38). Such systems of vacuoles sometimes occupy the greater part of the body of the cell so that only a small rim, usually containing the nuclei, remains (Figs. 38 and 39). The asteroids lying in these larger vacuoles have an irregular and deformed structure (Fig. 38), sometimes more or less disintegrating (Fig. 39). The development of asteroid bodies is often associated with more or less pronounced fatty change in the cytoplasm of the giant cells (Pl. IV B). Occasionally there is an increased density of the cytoplasm around the asteroid bodies and this may be laminated (Fig. 40). In the opinion of the present author this marks the first stage of their transition to Schaumann bodies.

In some cases there is precipitation of calcium and iron in the asteroid bodies. This usually begins in the centre of the bodies, where there may

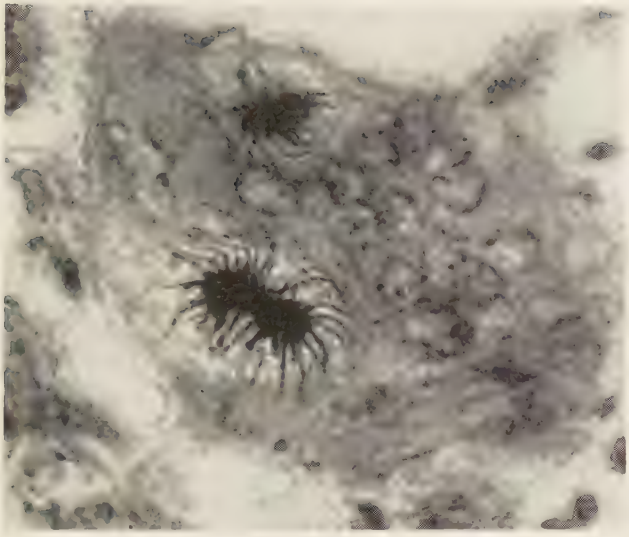


Fig. 36 (Case II: 28). Giant cell with two fully developed asteroid bodies. Orcein-methylene blue.

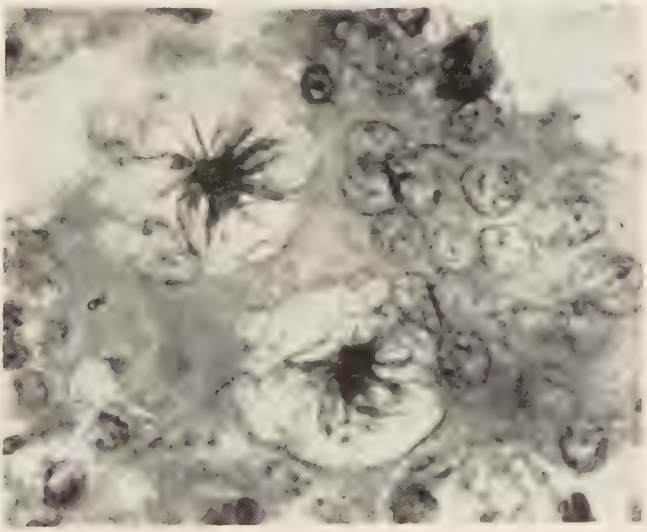


Fig. 37 (Case II: 28). Giant cell with two somewhat irregularly formed asteroid bodies lying in a system of vacuoles. Orcein-methylene blue.

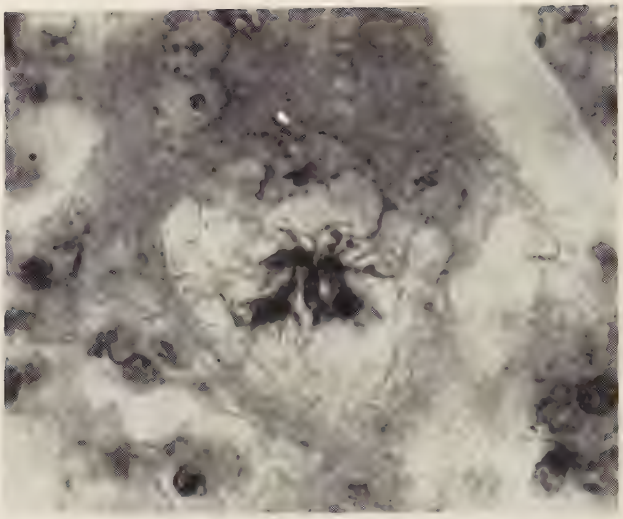


Fig. 38 (Case II: 28). Giant cell with a considerably distorted asteroid lying in a large system of vacuoles. Only a small part of the giant cell remains unchanged. Orcein-methylene blue.

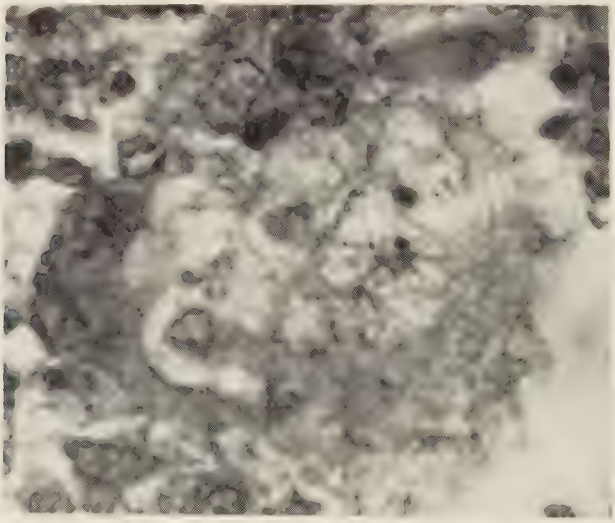


Fig. 39 (Case II: 28). Giant cell with numerous vacuoles occupying the greater part of the cytoplasm. Remains of an asteroid in the system of vacuoles. Orcein-methylene blue.

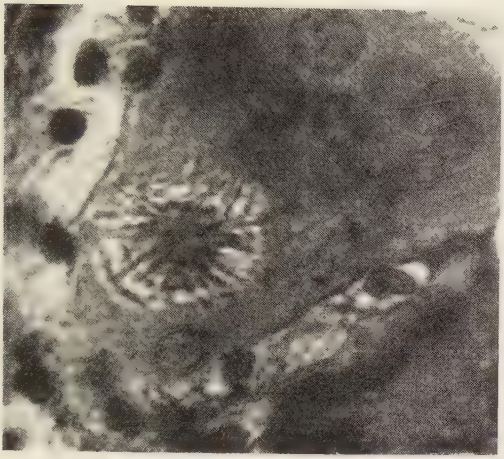


Fig. 40 (Case I: U. 825/42). Giant cell cell containing an asteroid in the periphery of which there are two concentric zones of precipitation, marking the first stage in its development into a Schaumann body. Htx.-v.G.

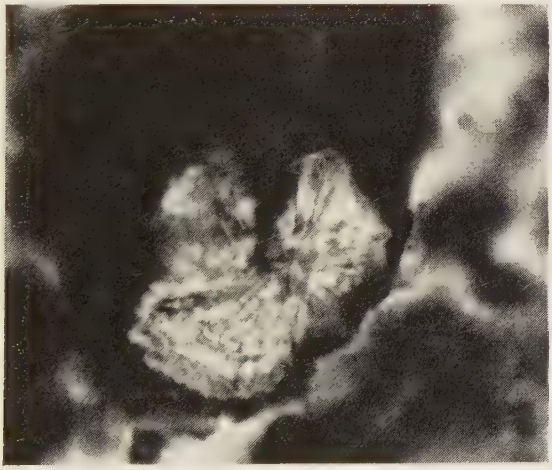


Fig 41 (Case I: U. 825/42). Giant cell with a calcified asteroid. The photograph is taken in polarised light.

occasionally be seen uncalcified remains of the formation (Fig. 13 d). The whole asteroid is gradually transformed into an anisotropic crystal with a star-shaped structure (Fig. 41). It may sometimes be seen how the encrustation with the iron and calcium salt spreads concentrically even into the nearer parts of the apparently unchanged cytoplasm.

This, however, is not seen in asteroids of which the surrounding cytoplasm is the seat of the vacuolar degeneration mentioned above.

The asteroids are slightly eosinophilic. With azan they stain red except in those cases where the rays are thin and slender, these usually stain greyish blue. Amyloid staining gives negative results. The asteroids cannot be stained with scarlet red or by Spielmeier's method, nor do they give positive results when stained for fibrin. The most suitable staining method for studying the morphology and pathogenesis of these structures is that using orcein, with which they stand out reddish brown. In Ziehl-Neelsen stained preparations they appear pink. The central rounded structures from which the rays emanate usually appear blue when stained with azan while the rays, as has been mentioned, stain red.

In the cases in which the asteroids have been transformed into anisotropic crystals the van Kossa and iron reactions are positive.

There are usually no centrospheres in those giant cells which contain two or more asteroid bodies.

Discussion

As was shown in the review of the literature, many opinions have been put forward as to the nature of the asteroids. The present author believes that they represent a protein precipitate in the enlarged microcentra of the giant cells. Several observations support this hypothesis.

The staining properties of the asteroids strongly suggest that they are, at least to a large extent, composed of protein. It would seem, however, to be difficult to assess the chemical composition of the protein on the basis of the staining reactions, for, as Apitz (1940) pointed out, it is not the chemical properties of the protein which determine its staining reactions but its colloid state. The fact that the asteroid bodies stain reddish brown with orcein does not, therefore, necessarily mean that they are composed of elastin as some previous authors have suggested. The absence of any sign of phagocytosis of elastin by the giant cells, and the fact that there is very little elastin in lymph nodes and what there is is mainly confined to the capsule and the vascular walls, makes it extremely improbable that the asteroids should be composed of this substance. It is true that the elastin in the tissues is destroyed in tuberculosis, and it is also evident that the Langhans giant cells sometimes phagocytose elastic fibrils. When these fibrils have been taken up by the giant cells, however, they look quite unlike asteroids.

On the other hand there is a great similarity between the asteroids and the enlarged microcentra of the giant cells. Thus their size is about the same and the central bodies and centrosphere are also seen in the asteroids although in a coarsened and distorted form (Fig. 34). Further support for this view that the asteroids arise as a result of the precipitation of protein in the enlarged microcentra, especially the centro-

spheres, is derived from a circumstance which has already been referred to, namely that a microcentrum is seldom seen in a giant cell which contains several inclusions.

As was shown before, the development of asteroids is associated with the appearance of fine droplets of fat in the protoplasm of the giant cells (Pl. IV B). It is probable that both this fatty change and the development of the asteroids are the expression of degeneration of the cells. In its more advanced stage this degeneration takes the form of marked vacuolisation of the giant cells leading to the disintegration of both the cells and the inclusions.

The author feels unable to answer the question whether the asteroids are formed from the protein of the degenerate giant cells themselves or from protein which has been taken up by them.

It has been shown that in certain cases calcification of the asteroids occurs. This must obviously take place before the degenerative process has gone so far that vacuoles have formed around the inclusion for the calcified asteroids always lie, as is shown in Fig. 13 a, in direct contact with homogeneous protoplasm. If the asteroid bodies can become transformed into Schaumann bodies, and assuming that this is a slow process, the tissue lesions in series I should, on the average, be older than those in the present series. There is some clinical support for this suggestion in that the average duration of the adenitis was longer in series I than in series II. On the other hand, if one tries to judge the age of the lesion by the degree of fibrous induration one finds no convincing evidence that the Schaumann bodies are characteristic of the advanced and the asteroid bodies of the recent lesions. On the contrary, one may find only asteroids, often with signs of disintegration, in cases which must clearly be old on account of the advanced stage of induration, while it is not infrequent to find only Schaumann bodies in lymph nodes in which the lesions are obviously recent. This poses the question whether or not the Schaumann bodies always originate from asteroids. As the observation that asteroids can become Schaumann bodies only applies to the few cases in which both types of inclusion are present it does not seem improbable that in these cases there is a coincidence of two mechanisms, one of which leads to the formation of asteroids and the other to that of Schaumann bodies. This hypothesis is further supported by the fact that in most of the Schaumann bodies there were no asteroid crystalline structures in the middle. The study of the formation of the Schaumann bodies does not either provide any evidence that they are always formed via preformed asteroid bodies.

It is noteworthy that in series I Schaumann bodies were found in 22.4 per cent of the cases and asteroid bodies in 5.2 per cent while the proportions are practically reversed in the present series. As already stated, it is also noteworthy that in the latter series Schaumann bodies are almost exclusively present in cases in which there is a marked clinical

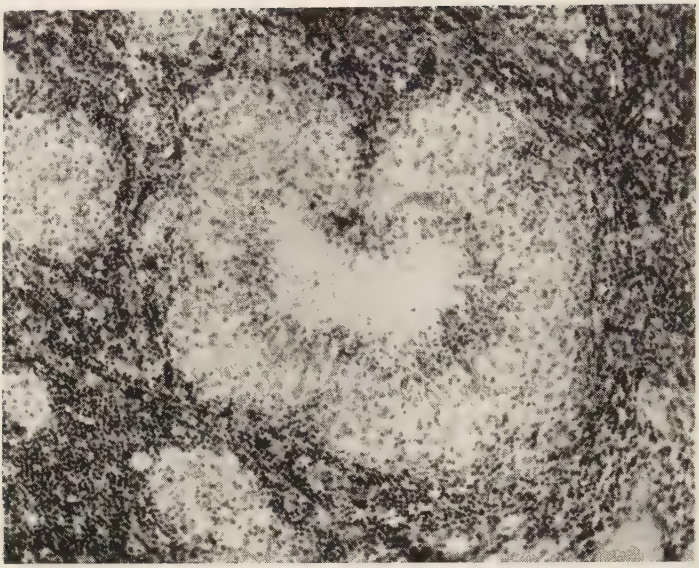


Fig. 42 (Case II: 50). An epithelioid cell granuloma showing central caseation. Htx.-v.G.

relationship to ordinary tuberculosis. In accordance with what has already been said about these cases it seems hardly possible to explain this except on the assumption that l.b. is a form of tuberculosis and that each of these types of inclusion is pathogenetically related to a particular degree of immunity to tuberculosis in the organism.

As to the microscopical differentiation between chronic hyperplastic tuberculosis and l.b., both types of inclusion seem to be helpful in that a tuberculoid process of the lymph nodes in which there are only Schaumann bodies *usually* represents the former condition while one in which there are only asteroids *always* represents the latter.

Regressive Changes

Caseous necrosis

True caseous necrosis only occurs to an insignificant extent in the centres of the granulomata in four cases (Fig. 42). Three of them were tuberculin negative. There is also a varying degree of necrobiosis in the central parts of the granulomata in 16 cases. In several of them this is so pronounced that they gave the pathologists the impression of being caseous necrosis. It is clear, however, that it is not a question of caseation. Thus, staining with azan, for example, reveals a more or less distinct mosaic structure of altered epithelioid cells. In the necrobiotic areas

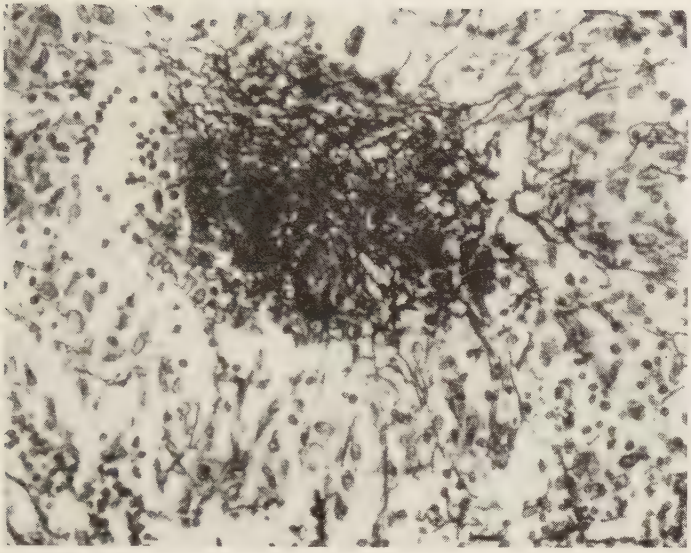


Fig. 43 (Case II: 15). Granuloma with central fibrillar (fibrinoid) necrosis. Note the transition of the precollagenous fibrils in the necrotic area. Wilder's reticulum stain.

occasional lymphocytes are sometimes seen. This necrobiotic lesion in the central parts of the granulomata seems more prevalent in those cases in which the lesions are relatively recent. For example, in case 34 one lymph node was removed for biopsy early in the disease and another later. There were marked necrobiotic lesions in the former and only a very slight amount in the latter.

Fibrillar (fibrinoid)necrosis

Fibrillar (fibrinoid)necrosis (Fig. 43) was found in 15 cases. However, the number of granulomata showing this change are fewer and the areas presenting it smaller in this series than in series I. For a description of the morphology and staining properties of this change see page 80.

Discussion

The investigations of the present author thus justify the conclusion that the presence of caseous necrosis does not exclude the diagnosis of l.b. It is, however, rare in comparison with fibrillar necrosis which is certainly often mistaken for caseous necrosis.

As fibrillar necrosis occurs in the form of tuberculosis already described as well as in l.b. no significance can be assigned to this change in the

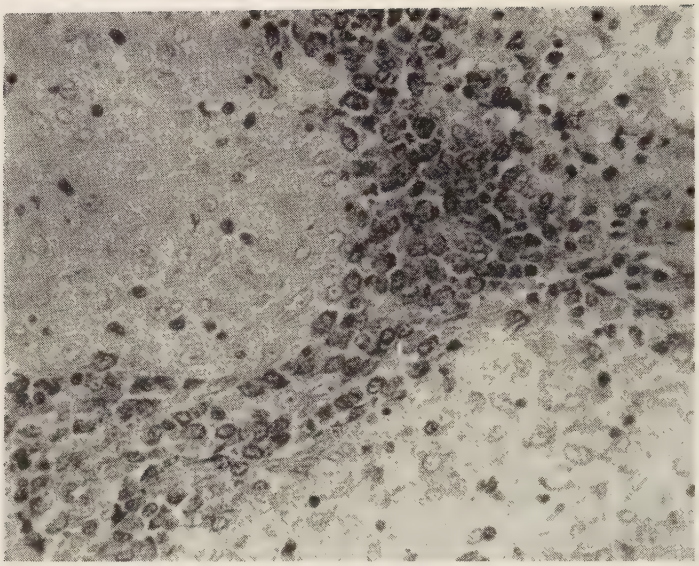


Fig. 44 (Case II: 26). Large number of plasma cells between two epithelioid cell granulomata. Ziehl-Neelsen.

differentiation between the two conditions. On the other hand, the fact that fibrillar necrosis is seen in both conditions should certainly be taken into account in assessing the etiology and pathogenesis of l.b.

According to present views the degree of hypersensitivity and the number of bacilli are the most important factors in caseation (Rich, 1951). Assuming that l.b. is a form of tuberculosis this might mean that the insignificant amount of caseation seen in the condition is due to a low degree of hypersensitivity, perhaps in association with only slight dissemination of bacilli. As already pointed out, the tuberculin testing also supports the idea that patients with l.b. have a low degree of hypersensitivity.

Perifocal Inflammatory Reaction

There is no perifocal reaction in the form of a lymphocyte barrier round the tubercles. As a result they appear to be sharply demarcated from the lymphoid tissue in so far as this has not been completely destroyed and replaced by thightly packed granulomata.

A type of cell which sometimes forms part of the microscopical picture in this series of nodes is the plasma cell. These are not, however, usually strictly perifocal in their localisation, but occur irregularly scattered in the form of foci between the granulomata (Fig. 44). In some places

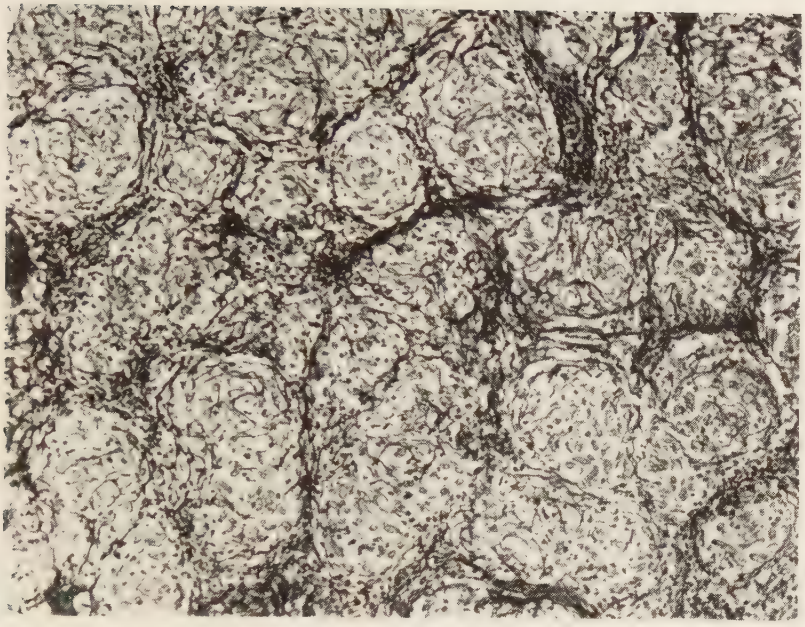


Fig. 45 (Case II: 38). Epithelioid cell foci without giant cells or caseous necrosis, lying close together. Granulomata traversed by a slender precollagenous reticulum. Wilder's reticulum stain.

one sees dense accumulations of plasma cells only. In some of the cases there is also a large number of mast cells and a great number of eosinophils. These are sometimes found in the granulomata but more often between them.

Discussion

According to the modern view, antibody proteins which are largely pathological globulins, are formed by the reticuloendothelial cells. Thus, Fagræus (1948) found that the formation of antibodies takes place during the transition of the reticulum cells into plasma cells. On the basis of these observations it seems justifiable to claim that there is a relationship between the occurrence of large numbers of plasma cells and that of hyperglobulinemia in l.b. and to regard them both as the expression of strong stimulation of the immune mechanisms. This view was also held by Teilum (1948) as has already been mentioned. He also supposed that the hyalinosis (paramyloidosis according to him) in l.b. is a morphological expression of the hyperglobulinosis in the reticuloendothelial system.

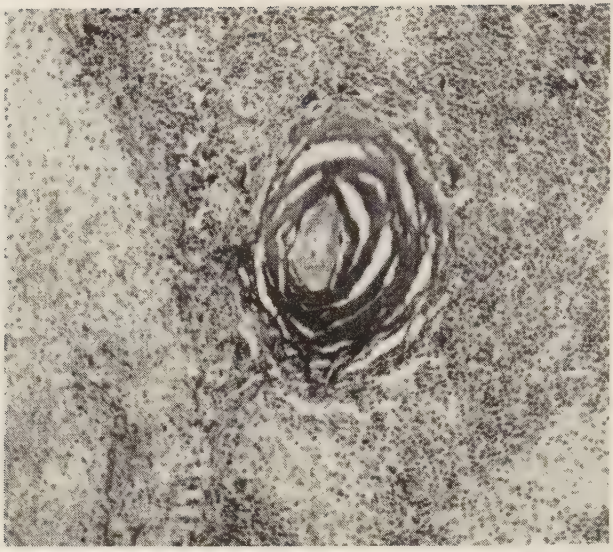


Fig. 46 (Case II: 25). Perivascular "onion peel hyalinosis". Htx.-v.G.

Indurative Changes

The indurative changes are essentially the same as those seen in series I. As in that series the tubercles are traversed by a rather fine precollagenous network (Fig. 45) which is often arranged concentrically at the periphery of the tubercles. There the interfibrillar spaces are frequently narrowed. The reticulum is occasionally fragmentary, probably because the granulomatous process is of recent onset. As the granuloma gets older the intercellular reticulum becomes coarser and closer. The intragranulomatous sclerosis is, on the average, more marked than in series I.

Alongside the intragranulomatous sclerosis there appears a perigranulomatous hyalinosis which is, in essence, the same as that described in series I. Lamellar perivascular hyalinosis ("onion peel hyalinosis") is rare and was only seen in one case (Fig. 46).

Induration of the granulomata gradually leads to their more or less complete transformation into connective tissue foci poor in cells and often hyalinised. As in series I this fibrohyaline induration does not take place simultaneously in all the tubercles. One may therefore see markedly hyalinised granulomata alongside others which are only slightly indurated (Fig. 47). The Langhans giant cells seem to be most resistant to this induration and they may not infrequently be seen as the sole surviving remnants of the granulomatous tissue.

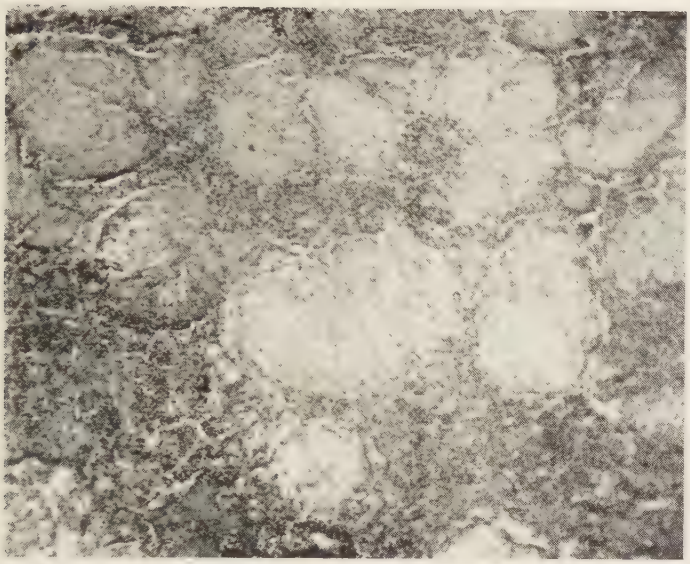


Fig. 47 (Case II: 13). Tubercles with varying degrees of fibrosis and fibrohyaline induration. Htx.-v.G.

Discussion

The present author considers that there are very good grounds for Teilum's hypothesis concerning the pathogenesis of the hyalinosis and the nature of the hyalin seen in l.b. As has already been shown, however, a fibrohyalinosis similar in all respects also occurs in chronic hyperplastic tuberculosis. There too it is associated with the presence of large numbers of plasma cells and in the three cases in which a determination of the serum protein was made hyperglobulinemia was also found. Under these circumstances it seems justifiable to extend Teilum's hypothesis as to the pathogenesis of the lesions in l.b. to include that of the lesions of chronic hyperplastic tuberculosis as well, a form of tuberculosis which resembles l.b. in many other respects too.

Vascular Lesions

The tubercles in the present series, as in series I, are largely perivascular in arrangement. Only in occasional cases, however, are lesions seen in the vessels surrounded by granulomatous tissue, and such as were present took the form of hyalinisation of the vascular wall, sometimes in association with thrombotic occlusion of the lumen. The vas-

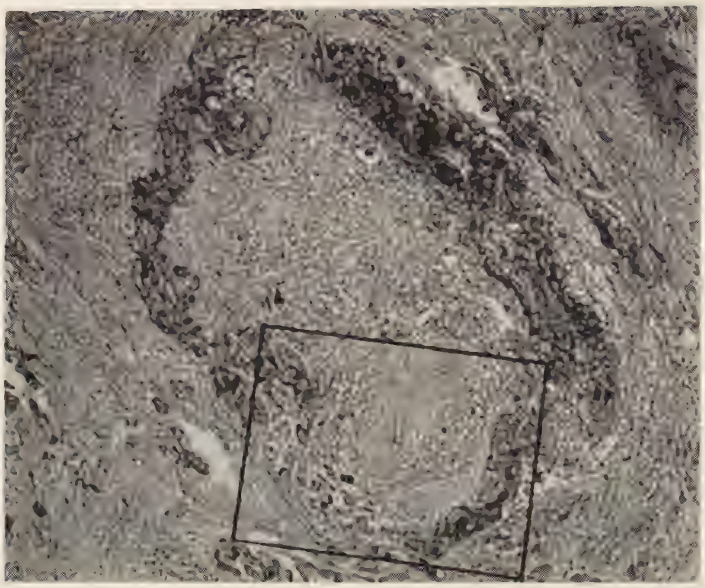


Fig. 48 (Case II: 33). A pulmonary vessel with marked destruction of the wall by granulomatous tissue composed of epithelioid cells and Langhans giant cells. Orcein-methylene blue.

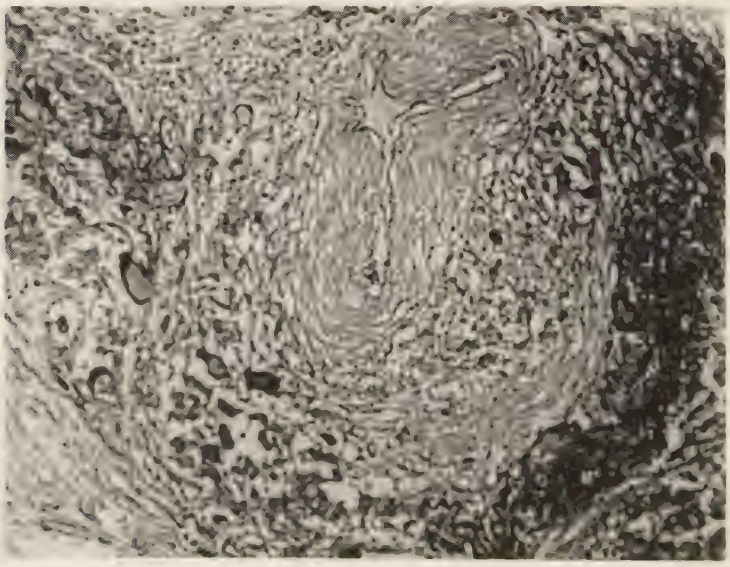


Fig. 49 (Case II: 33). Higher magnification of the enclosed part of Fig. 48.

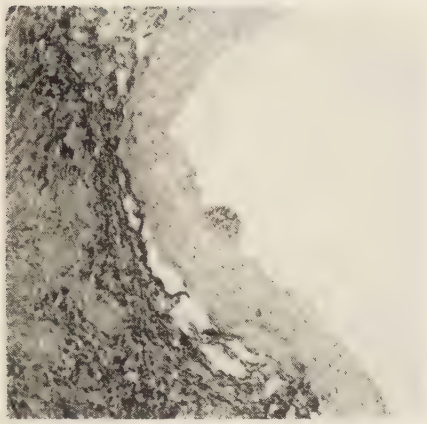


Fig. 50 (Case II: 33). Artery of the lung with a small intimal tubercle. Htx.-v.G.

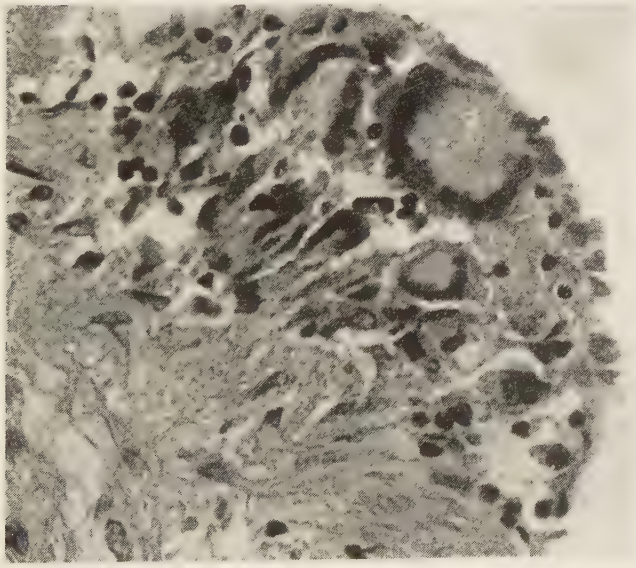


Fig. 51 (Case II: 33). Higher magnification of the intimal tubercle shown in Fig. 50.

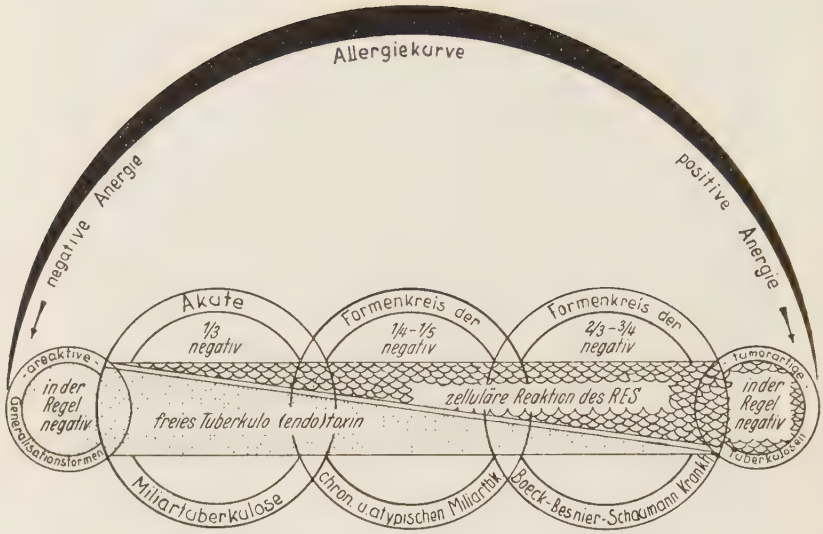


Fig. 52. Schematic representation of the relation between the tuberculin reaction and the reaction of the reticuloendothelial system in different kinds of tuberculosis. (Courtesy of F. Schmid.)

cular changes were more striking in the lungs in case 33 where they took the form of widespread destruction of the walls of the vessels with invasion by granulomatous tissue (Figs. 48 and 49). Small intimal tubercles composed of epithelioid cells and giant cells (Figs. 50 and 51) were also seen in one or two medium sized branches of the arteries of the lungs.

Etiological Investigations

About 900 Ziehl-Neelsen stained sections of lymph nodes were searched with the greatest thoroughness without any acid-fast rods being seen in the tubercles. On the other hand, acid-fast bacilli were found in two instances (case 21 and 28) but only in nodes examined after ordinary tuberculosis had supervened.

Sixteen lymph nodes were examined for viral inclusion bodies using phloxine-methylene blue staining but none were found.

In 19 cases the lymph node contained the structures demonstrated by Hollström and which he considered to be fungal cells. The present author does not consider that these play any part in the etiology of l.b., partly because they were also seen to a great extent in the nodes in series I and in normal nodes especially in old people. A more detailed description of these structures will be given in another connection.

CHAPTER 10

General Discussion and Conclusions

As already stated, the chronic hyperplastic form of tuberculosis is identical with the large-celled hyperplasia described by Ziegler. The present work shows that this form of tuberculosis has been largely misdiagnosed by both clinicians and pathologists as l.b. This undue preference for the diagnosis of l.b., probably not confined to Sweden, is due to the fact that physicians have not been sufficiently well aware of the existence of a form of tuberculosis very similar to l.b. but not identical with it. As far as the present author can tell, the only worker who has expressed a correct opinion as to the relationship between l.b. and the Ziegler form of tuberculosis is Lindau (1928) who wrote: "Of the acknowledged forms of tuberculosis it [l.b.] appears to be most nearly related and similar to Ziegler's tuberculous large-celled hyperplasia."

It is a distinguishing feature of chronic hyperplastic tuberculosis, as has been shown, that there is more or less widespread enlargement of the peripheral lymph nodes without any tendency to liquefaction or fistula formation, and also that its course is protracted without the general condition being affected to any great extent. Another similarity to l.b. is seen in the fact that there is hilar enlargement, sometimes in association with bilateral parenchymatous changes. These may be combined with a low sensitivity to tuberculin. In some cases of this form of tuberculosis as in l.b., there is hyperglobulinemia and monocytosis.

The microscopic picture of chronic hyperplastic tuberculosis is also, as has been shown, very similar to that of l.b. The morphological unit is the same in both cases, i.e. the tubercle composed mainly of epithelioid cells. The two conditions also have in common the almost complete absence of caseation. On the other hand, fibrillar necrosis is common in both of them. Furthermore, the presence of inclusion bodies in the somewhat atypical Langhans giant cells is distinctive of both conditions. The induration, too, which appears as the lesions grow older is of the same nature in the two. Finally, in both conditions, but especially in l.b., there is a large number of plasma cells in the affected lymph nodes.

From the pathogenetic aspect, also, there are certain similarities between chronic hyperplastic form of tuberculosis and l.b. In both instances the primary infection usually seems to be in the lungs. In spite of this no parenchymatous lesion of the lungs, primary to the hilar

changes, has been found radiographically in l.b. nor in cases of chronic hyperplastic tuberculosis showing active lesions of the hilar nodes. Further, in both conditions the infection seems to spread by both the blood and lymph.

The great likenesses in many respects between chronic hyperplastic tuberculosis and l.b. may lead one to ask oneself what, exactly, is the difference between them, and what features point the way to the differential diagnosis. As far as the symptomatology is concerned, it is not any individual symptom which is characteristic of l.b., but rather the grouping of the symptoms. Judging from the present investigation, however, there are a few symptoms which occur in l.b. but not in chronic hyperplastic tuberculosis, e.g. bilateral parotitis and osteitis multiplex cystoides. The presence of one of these symptoms is therefore of especial value in the clinical differentiation between the conditions.

As already stated, however, the course of l.b. is by no means always polysymptomatic. There may often be difficulties in the differential diagnosis between it and chronic hyperplastic tuberculosis, especially in cases presenting bilateral hilar enlargement as their only symptom, for this symptom may occur in either condition. Neither will the association of this radiographic change with a low sensitivity to tuberculin make the diagnosis of l.b. certain. Even if the opportunity of examining an affected peripheral lymph node arises in such a case it is not always possible to make a firm diagnosis on the basis at the tissue lesions. Therefore, it is difficult to draw a line between the two conditions.

While there is no microscopical structure pathognomonic of chronic hyperplastic tuberculosis or l.b. it has been shown that the two conditions can be differentiated to some extent on the basis of the general pattern of the lymph nodes. While the former condition is usually characterised by a relatively sparse scattering of rosette-shaped conglomerates of tubercles of somewhat varying size, the tubercles in the latter condition are usually more uniform in size, and although they generally lie closer together and commonly occupy the whole of the parenchyma of the lymph node, yet they are, as a rule, separate from one another. Thus, the microscopical picture of l.b. is usually more monotonous than that of chronic hyperplastic tuberculosis. As has been shown already, however, there are a few nodes in each of series I and II which are intermediate in general pattern between the two basic types just described. In such cases, it is impossible to base a firm diagnosis on the general pattern alone.

Another dissimilarity between l.b. and chronic hyperplastic tuberculosis refers to the type of giant cell inclusion. The Schaumann body is the inclusion body most commonly seen in the lymph nodes of chronic hyperplastic tuberculosis, while the asteroid body is the inclusion most characteristic of l.b. This fact is, as has already been pointed out, of some help in the differential diagnosis.

Other differences between the two diseases under consideration seem to be differences in degree rather than in kind. For example, the regressive changes in the tubercles are somewhat more pronounced in hyperplastic tuberculosis than in l.b. while the opposite is true as regards the degree of intragranulomatous sclerosis. One gets the impression that these differences are essentially due to the greater reactive capacity of the reticuloendothelial system in l.b. than in chronic hyperplastic tuberculosis. On the basis of the considerable morphological similarity between the two conditions the present author feels justified in extending Teilum's hypothesis concerning the morphogenesis in l.b. to include the chronic hyperplastic form of tuberculosis.

Concerning the etiology of l.b., it has already been pointed out that there are certain features of the condition which suggest that it is not tuberculous in nature. The most important of these are that the patients do not come from tuberculous environments, that the sensitivity to tuberculin is low during the course of the disease and that it is relatively seldom possible to demonstrate tubercle bacilli in the lesions. A closer examination of these arguments, however, shows that they can be used equally well in favour of the tuberculous origin of l.b. as against it.

As Schaumann himself pointed out, the fact that tuberculosis is rare among the persons closest to the patients suffering from l.b. may well be due to the fact that they themselves and their closest relatives have a constitutional resistance to tuberculosis. In accordance with this view l.b. would be the form of tuberculosis developed by those most resistant to tuberculosis. The frequent occurrence of the disease in siblings, often with a similar course, may support this view. The fact, reported by Löfgren and Lundbäck (1952) and already mentioned, that tuberculin negative patients with l.b. differ from tuberculin positive ones with a similar family history of tuberculosis in that they show practically no signs of previous tuberculous infection also supports the view that a strong resistance is an important factor in the pathogenesis of l.b.

Neither does the fact that the tuberculin sensitivity is low in l.b. conflict with the view that this is a tuberculous condition, for it has been shown that in a few cases of chronic hyperplastic tuberculosis the tuberculin sensitivity is also low. Furthermore, the fact that l.b. patients who originally gave a negative tuberculin reaction usually showed a positive one with the onset of classical tuberculosis or that, as the present author has shown, the sensitivity to tuberculin increased with the onset of an exudative phase in the condition, both suggest that l.b. is a form of tuberculosis. The cause of the low tuberculin sensitivity seems, however, to be obscure. It would not seem to be improbable that it is associated with the great reactive and proliferative capacity of the reticuloendothelial system. This suggestion is illustrated by Fig. 52 taken from Schmid's work *Die generalisierten Tuberkulosen.*

As far as the third argument, the difficulty in demonstrating tubercle

bacilli, is concerned, it must be admitted that the number of positive findings is relatively small. But this surely does not justify one in denying them any significance. Table 1 shows that in most of the cases in which the guinea pig test was positive there was something atypical about it. Tuberculosis either developed unusually slowly or appeared only in some of the inoculated animals. This suggests that the bacilli in the inoculum were relatively avirulent. In the present series of l.b. a guinea pig test was carried out with a positive result on the sputum in case 5. The fact that the patient had been treated in a sanatorium for some time before the test was performed, however, deprives it of some of its value concerning the etiology of l.b. It is, however, worthy of note that tuberculosis only occurred in the animal which had received an intraperitoneal injection and not in the one which had been injected subcutaneously. Further, the occurrence of tubercle bacilli in the sputum of the patient was not accompanied by the appearance of new pulmonary changes atypical of l.b. Furthermore, tubercle bacilli and acid-fast rods were found in the lymph nodes in cases 21 and 28 respectively in the same series, but not until classical tuberculosis had supervened. The sudden appearance of miliary tuberculosis in case 21, the fact that it manifested itself in the form of bilateral hilar enlargement with bilateral parenchymatous changes characteristic of l.b., and the fact that it affected the lymph nodes previously involved by l.b., all suggest that l.b. and classical tuberculosis are but two phases of the same disease.

As seen from the literature the development of classical tuberculosis, especially miliary tuberculosis, is common in l.b. This is also in complete agreement with the experience that tuberculosis is the commonest cause of death in l.b. Of 59 autopsy cases of l.b. collected by Ustvedt (1948), tuberculosis was found to be the cause of death in eleven. However, he comments that "18 per cent of death of tuberculosis does not seem very high", an opinion which can hardly be accepted as correct. As the present study shows, the incidence of fatal tuberculosis is even greater in l.b. than in the chronic hyperplastic form of tuberculosis. Assuming that l.b. is a form of tuberculosis, and in view of the fact that the disease spreads partly by the blood stream, it seems reasonable to consider the numerous cases of miliary tuberculosis occurring in patients suffering from l.b. as having been caused by the dissemination of an unusually large number of bacilli, perhaps in association with a temporary lowering of the patient's resistance.

The strongest support for the opinion that l.b. is a form of tuberculosis is, perhaps, the fact that it is the only granulomatous disease prevalent in this country which shows a marked similarity to tuberculosis, especially the hyperplastic form described here, both in its symptomatology and in its microscopic picture. The similarities between them are, in fact, so remarkable that it seems justifiable to consider the chronic hyperplastic tuberculosis as an intermediate form between classical tuberculosis

and l.b. The differences between the two conditions can, as has already been pointed out, be explained by the fact that the defence reaction of the reticuloendothelial system is greater in l.b. than in the hyperplastic form of tuberculosis.

The opinion that in l.b. the reticuloendothelial system has a greater capacity to destroy tubercle bacilli is supported by several observations of earlier authors. Thus, by repeated biopsies Kyrle (1910) was able to show that the very earliest skin lesions in a case of l.b. contained tubercle bacilli but that these were soon destroyed and had completely disappeared from the tissue even before the specific skin lesions had fully developed. Furthermore, Warfvinge (1945) observed that intracutaneous injection of dead tubercle bacilli in tuberculin negative patients with l.b. elicited a tissue reaction similar to that of this disease. He also found that the tubercle bacilli injected were faster destroyed in these patients than in those suffering from classical tuberculosis. It thus seems reasonable to suppose that the acid-fast rods observed by several workers in the lesions in l.b. represent the remains of a larger number originally present.

As to the pathogenesis of l.b., it is clear, for various reasons, that it is not a classical primary tuberculous infection but a form of primary tuberculosis running an atypical and slow course with affection of the hilar lymph nodes as its chief and most constant symptom. The infection would seem to spread via the lymphatics, in the first place to the other mediastinal nodes and to those of the neck, and also by the blood. As the patients seldom die in the florid stage of the disease little is known about the pathological anatomy of the enlarged hilar nodes seen in radiograms. There are, however, a few instructive autopsy cases reported which throw light on the etiology and pathogenesis of the disease. Thus, Granström *et al.* (1946) described a tuberculin negative case of l.b. with uveoparotitis in which microscopical examination of the mediastinal lymph nodes revealed caseation and acid-fast rods. A guinea pig test using material from such a lymph node gave a positive result. In another case reported by Mylius and Schürmann (1929) the Pirquet test was negative and there were characteristic changes in the lungs, bones, eyes and elsewhere. Microscopical examination of the mediastinal lymph nodes revealed scanty caseation. A guinea pig test using material from such a node gave a positive result in so far as two of the five inoculated animals died of generalised tuberculosis spreading from the site of inoculation (see Tab. 1.). The present author therefore considers that *the observations made in the present investigation, taken together with those of previous workers, indicate that l.b. is a form of tuberculosis.*

Summary

The term lymphogranulomatosis benigna (l.b.) refers to a complex of symptoms described by the Swedish worker Schaumann in 1914. It is distinguished, as a rule, by bilateral pulmonary lesions and more or less generalised swelling of the lymph nodes, often combined with low sensitivity to tuberculin. In some cases there is also enlargement of the spleen and liver, swelling of the parotids, eye lesions and changes in the bones. Neurological signs occasionally occur. The disease not seldom begins with erythema nodosum, joint pains and fever. Other common signs are elevation of the sedimentation rate, hyperglobulinemia, eosinophilia and monocytosis. The syndrome, often called sarcoidosis in the U.S.A., practically never occurs in persons below the age of twenty but reaches its peak incidence in the age group 25 to 30 years. Generally the clinical signs of the disease disappear in a couple of years, but about every tenth case runs a chronic course.

Microscopically, l.b. is characterised by sharply defined foci of epithelioid and giant cells. Caseation occurs but only rarely. As time goes on the granulomata show a strong tendency to fibrous induration.

Despite the great similarity of the microscopical picture to that of tuberculosis, Schaumann did not discuss the histological differential diagnosis between l.b. and the forms of tuberculosis which the German workers, in particular, call atypical. The best known of these atypical forms of tuberculosis is the large-celled hyperplasia described by the German pathologist Ziegler (1890). The likeness between it and l.b. eventually led to a discussion regarding the connection between the two. Different opinions were expressed. Some authors asserted that despite the microscopical similarity of l.b. to the aforementioned form of tuberculosis, it is an independent entity. Others claimed that the tissue lesions described by Ziegler are the histological counterpart of the clinical concept of l.b.

The aim of the present investigation was to clear up the question of the relationship between l.b. and tuberculosis, including the Ziegler form of tuberculosis.

Chapter 1. The study is begun with an historical outline of the research on the l.b. syndrome.

Chapter 2 deals with the bilateral hilar lymphoma syndrome (the BHL syndrome: Löfgren, 1946) given particular study by Swedish workers and the investigations concerning the relationship between it

and l.b. These investigations have shown that the BHL syndrome is nearly always an early manifestation of l.b.

Chapter 4. Review of the literature regarding the histopathological features of l.b. and the microscopical differential diagnosis. In 1914 Schaumann said that the absence of caseation was a distinctive feature of l.b. It appeared later, however, that caseation occasionally did occur in l.b. and so disappeared one of the most important criteria of the disease. It was then studied whether l.b. had any other histological features which could be used in order to distinguish it from tuberculosis. It was observed that the epithelioid cells differed from the ones in classical tuberculosis and not seldom contained inclusion bodies, sometimes a concentrically laminated type (Schaumann body) and sometimes a stellate formation (asteroid body). These bodies, as several authors have supposed, seldom or never occur in classical tuberculosis. Furthermore, Ricker and Clark (1949) described a form of necrosis which they considered to be characteristic of l.b., so-called fibrinoid necrosis. Several workers also stated that the epithelioid cell foci in l.b. were traversed by a precollagenous reticulum never seen in tuberculosis, and that the induration was more pronounced in l.b. and of a partly different nature than in tuberculosis. The Danish pathologist Teilum (1949) drew attention to a characteristic form of perigranulomatous and perivascular hyalinosis distinctive of l.b. In his opinions these lesions were caused by an allergic hyperglobulinosis in the reticuloendothelial system due to persistent or repeated stimulation of immune mechanisms. In support of this hypothesis he adduced the hyperglobulinemia and abundance of plasma cells in l.b.

Chapter 5 gives an account of the various opinions regarding the origin of l.b. Particular attention is given to the arguments for and against a tuberculous origin. The reports regarding the finding of bacilli in l.b. are presented in tabular form.

Chapter 6. The present author studied a large number of lymph nodes showing tuberculoid lesions. The nodes were divided into two series according to whether or not acid-fast bacilli were seen in the microscopical sections. The one series in which bacilli were found was assumed to be representative of Ziegler's large-celled hyperplasia, the other in which no bacilli were demonstrated was considered to be l.b. In order to form an opinion as to whether or not the lesions were of tuberculous origin in the latter series, despite the absence of bacilli, the clinical and histopathological features of the two series were compared.

Chapter 7 contains an account of the composition and origin of the material and the primary microscopical diagnosis. The material was divided into: –

Series I: Lymph nodes containing bacilli (59 specimens from 58 patients)—*tuberculosis chronica hyperplastica* (Ziegler's large-celled hyperplasia).

Series II: Lymph nodes without bacilli (54 specimens from 50 patients)—*lymphogranulomatosis benigna.*

Chapter 8 contains an analysis of series I. In these cases there was a protracted swelling of one lymph node or a group of nodes, situated on the neck in the great majority of cases. The patients had very little symptoms. The sedimentation rate was practically normal. There was no periadenitis of note. Liquefaction and fistulas did not occur.

There was a family history of tuberculosis in 26 per cent of the cases. In 21 per cent pulmonary calcification was observed and in 19 per cent there was a previous history of manifest tuberculosis. In 4 cases the present affection of the lymph nodes was a relapse of classical tuberculous lymphadenitis. Follow-up of 31 patients revealed no death from tuberculosis.

In 7 cases there was an active pulmonary process of clinically obscure origin. In 5 of them it was a question of bilateral hilar enlargement, in one case combined with bilateral parenchymatous lesions. In the sixth case there was only unilateral hilar enlargement and in the seventh only bilateral lesions in the pulmonary parenchyma. Both patients with lesions in the pulmonary parenchyma gave a negative response to 1 mg of tuberculin. Monocytosis was present in 4 cases, and hyperglobulinemia was noted in the two cases in which the serum protein was determined. None of the 31 patients followed up had acquired l.b.

The lymph node lesions were generally characterised by a fairly even dissemination of rosette-shaped groups of tubercles. Only a few nodes showed the pattern characteristic of series II. Both the epithelioid cells and the occasional giant cells exhibited enlargement of the microcentra. Several of the giant cells resembled foreign body giant cells. Twenty-two per cent of them contained Schaumann bodies and 5 per cent asteroid bodies. The first type of inclusion seems to be a sign of advanced cellular degeneration and is considered as an autochthonous concrement resulting from precipitation of protein with deposition of salts in the precipitate. — Mild degree of caseation occurred in the centre of the tubercles in 12 cases. On the other hand, the type of necrosis described by Ricker and Clark in l.b. occurred in not less than 40 cases. It is thought to develop through the permeation of the precollagenous reticulum with cellular disintegration products. This type of necrosis, which should be distinguished from caseation, can be called fibrillar necrosis. — The perifocal inflammatory reaction was insignificant in the great majority of nodes. A relatively large amount of plasma cells occurred in groups between the tubercles. — There was a strong tendency to induration of the tubercles. They were traversed by a slender precollagenous network sometimes arranged in concentric fashion. As the process grew older, the reticulum became coarser and fibrohyaline induration converted the tubercles to foci of fibrohyaline connective tissue poor in cells. — Several tubercles were situated around the vessels but the latter showed any lesion. On the

other hand, in a couple of cases arteritis and intimal tubercles were seen in the vessels not surrounded by tubercles.

Acid-fast bacilli occurred sparsely in the granulomatous tissue. About 240 slides had to be examined to find one bacillus in each of these cases. In about 50 per cent the bacilli were situated in the giant cells. Only in one case was lymph node tissue available for a guinea pig test; it gave a positive result.

The author concludes that the nodes in this series are affected by a benign form of tuberculosis, caused in most cases by lymphatic dissemination of the tubercle bacilli from a focus of primary infection. He also concludes that this form of tuberculosis is the same as the large-celled hyperplasia described by Ziegler and shows that it also occurs in other organs. He suggests that a better name for this condition would be *chronic hyperplastic tuberculosis*.

Chapter 9 gives the results of the analysis of series II. This series differs from the foregoing one in having a greater variety of clinical features and more spread involvement of the lymph nodes. In 7 cases the disease began with erythema nodosum and in 3 of them the erythema recurred. Erythema induratum occurred in one case. Forty-three of the 49 patients whose lungs were X-rayed showed the pulmonary changes characteristic of l.b. In 3 of the 43 cases hilar adenitis was originally unilateral. Pleuritis occurred in 5 cases. In 3 of the remaining cases no pulmonary lesions could be demonstrated during the course of the disease and in the 3 others the pulmonary lesions were not wholly characteristic of l.b.

The enlargement of the peripheral lymph nodes was general in 16 cases. Liquefaction and fistulas were just as uncommon in this series as in the previous one. The nodes had the same gross appearance as in the foregoing series. Several other signs and symptoms characteristic of l.b. were noted. The sedimentation rate was elevated in the majority of cases. Eosinophilia, monocytosis and hyperglobulinemia occurred in several cases. Twenty-six per cent of the patients tested with tuberculin reacted positively to 1 mg. One patient showed a rise in tuberculin sensitivity in connection with the development of exudative pericarditis, another in connection with the development of miliary tuberculosis.

As regards the clinical relationship to classical tuberculosis only 9 per cent of the patients had a family history of tuberculosis. Only one had previously had manifest classical tuberculosis. Likewise only one case exhibited pulmonary calcification. On the other hand, at least 4 of the 36 patients followed up after about the same length of time as the ones in series I had acquired classical tuberculosis, and 3 of them died of the disease.

Microscopically, the lymph nodes generally exhibited a dense accumulation of submiliary to miliary foci of epithelioid and giant cells. As a rule, the pattern was more monotonous than in the first series. Some

nodes, however, showed the general pattern prevalent in series I. Not even when the tubercles lay close to one another did they show any tendency to coalesce. The epithelioid cells looked the same as in series I. The giant cells, generally of sparse occurrence, resembled foreign body giant cells to a certain extent, as was the case in series I. Schaumann bodies were seen in 5, or 10 per cent, of the cases. In 4 of these 5 cases, there was a relation to classical tuberculosis. Asteroid bodies were encountered in 14, or 28 per cent, of the cases. The morphological and staining properties are described in detail. The author believes that they develop through precipitation of protein in the enlarged microcentra of the giant cells. Their relation to the Schaumann bodies is discussed and likewise their significance in the differential diagnosis. — True caseous necrosis occurred in only 4 cases, 3 of which gave a negative tuberculin reaction. Fibrillar (fibrinoid) necrosis was seen in 15 cases. The perifocal inflammatory reaction was of insignificant degree, as in series I. Large quantities of plasma cells were observed between the tubercles in many instances. The connection between the presence of these cells, the hyperglobulinemia and the indurative changes is discussed. The latter were of the same kind as in series I. The vascular lesions, too, were of essentially the same nature as in series I.

Chapter 10 contains a summary and conclusions. The study has shown that the chronic hyperplastic form of tuberculosis (Ziegler's large-celled hyperplasia) is not identical with l.b. However, the great resemblance between them, which sometimes makes it hard or even impossible to draw a distinct line between them, would indicate that l.b. is also a form of tuberculosis. The chronic hyperplastic form of tuberculosis is probably the intermediate form between classical tuberculosis and l.b.

The microscopical differentiation, at least as regards lymph nodes, can be based to a certain extent on differences in the general pattern, but neither of the conditions has a distinctive structure of its own which can be used for differentiation. However, the occurrence of asteroid bodies *only* is distinctive of l.b. as opposed to the chronic hyperplastic form of tuberculosis. Otherwise, the differences between the two seem to be differences in degree rather than in kind and could be explained by a different intensity of reaction to the tubercle bacillus and its disintegration products. In the opinion of the author a strong reaction by the reticuloendothelial system causing rapid and usually complete destruction of the bacilli gives rise to the lymphogranulomatous condition.

In consideration of his own results and the observations of previous workers, the present author does not agree with arguments against the tuberculous theory. The fact that the patients suffering from l.b. so seldom came from a tuberculous environment seems to be compatible with the theory that it is the form of tuberculosis characteristic of the persons most resistant to this disease. The low tuberculin sensitivity in l.b. can just as well be used as an argument for as against a tuberculous

origin for the disease, especially as a low tuberculin sensitivity occasioally occurs also in the chronic hyperplastic form of tuberculosis. Further, tubercle bacilli are not uncommonly demonstrated in l.b.—an important fact to be considered in discussions on the origin of this syndrome. In addition, the fact that ordinary tuberculosis is a common cause of death in l.b. would also indicate that l.b. is of tuberculous origin.

As regards the pathogenesis of l.b., it seems probable that it mostly represents an atypical and slowly progressing form of primary tuberculosis.

This investigation was supported by grants from the Medical Faculty of the University of Uppsala and from the Swedish Medical Research Council.

Case Reports

Series I

Lymph Nodes with Bacilli Present. Tuberculosis Chronica Hyperplastica

Case 1. ♂, born 1900. No heredity for tuberculosis. Treated in hospital in 1936 with a diagnosis of myocarditis and in 1937 on account of enlargement of lymph nodes in the left axilla which had persisted for 4 months. They caused no discomfort. On admission his general condition was good and he had no fever. *Local condition:* A hard, painless lymph node the size of a hazel nut in the left axilla. Many hard nodes in both groins. *Operation:* Extirpation of the node in the left axilla. *Microscopic examination V. 1248/37* (I. Behring, M.D.): The whole lymph node is studded with tubercles of epithelioid cells, a few of which show central necrosis. No Langhans' giant cells. The picture is identical with that described under the names of *Boeck's sarcoid,* or *lymphogranuloma benignum.*

Case 2. ♀, born 1861. Treated in hospital in 1937 under the diagnosis of tuberculous lymphadenitis of the neck (lymphogranulomatosis benigna?) + ventral hernia through a scar. Sought advice on account of diffuse abdominal pain. On investigation a firm elastic node the size of a walnut was found in the neck below the right side of the jaw. It had been present for two years. During the previous few months a packet of nodes the size of a hen's egg had developed posterior to this and outside the angle of the jaw. The nodes in this packet were separate from one another. They were not tender but were firm and elastic. The skin was not adherent but they were fixed to the underlying tissues. *Operation:* Removal of a lymph node from the neck. *Microscopic examination U. 2102/37* (Prof. Gellerstedt): The whole node is diffusely infiltrated with small epithelioid cell tubercles of generally uniform size. Langhans' giant cells are only to be seen occasionally and are rudimentary. There are only traces of caseous necrosis. The whole process is quite recent and there is no sign of sclerosis or induration. *Patho-anatomical diagnosis:* Atypical tuberculosis. — *X-ray of lungs:* No abnormality of the sinus or diaphragm. There is considerable enlargement and increase in density of the hilar regions on both sides and the glandular shadows in them reach, on the right side, down to the diaphragm. The trachea seems to be displaced to the right. No definite changes in the parenchyma. *X-ray of bones of hands and feet:* Mild, diffuse decalcification (senile?), otherwise no abnormality. No information is available as to guinea pig tests or tuberculin reaction. *WR:* negative. *Final note:* "There is much to suggest that we are dealing with a case of lymphogranulomatosis benigna."

Case 3. ♂, born 1900. A daughter suffers from tuberculosis. Operated on at the age of 23 for enlarged lymph nodes on the right side of the neck. Two years later noticed enlargement of the nodes of the left side of the neck. Treated as an out-patient in 1937. *Operation:* Extirpation of a lymph node on the left side of the neck. *Microscopic examination U. 2164/37* (Prof. Gellerstedt): The whole lymph node is tightly packed with tuberculous granulation tissue in the form of fairly uniform submiliary epithelioid cell tubercles. Occasional giant cells are present

but their formation is rudimentary. Furthermore, there are only traces of caseous necrosis to be seen in one or two places. On the other hand, there is a striking tendency to hyaline sclerosis and thickening of the basic reticulum of the node. It thus presents the appearance seen in the relatively early stages of Schaumann's disease. It would be interesting to find out whether the patient presents the other symptoms of this condition. *Patho-anatomical diagnosis:* Atypical tuberculosis. *X-rays of lungs:* Normal.

Case 4. ♀, born 1919. Treated in hospital in 1937 for a buccal abscess and lymphadenitis of the neck (lymphogranuloma benignum). Three weeks earlier she had had a pimple on the left cheek. For three days she had had some pain and the whole cheek had swollen up. Her temperature never rose above 37.8° C. She had had a swelling on the right side of her neck for six years. She did not think it had grown larger. Treated with X-rays. *On admission:* General condition good. Temp. 37.3° C. *Local condition:* The left cheek was moderately swollen with oedema of the lower eyelid. In the middle of the cheek there was an area of infiltration about the size of a walnut. It was firm, slightly tender and showed superficial fluctuation. The overlying skin was reddened and in the middle there was a perforation the size of a pin head. Under the angle of the jaw on the right side there was a firm, painless, moveable tumour the size of a pigeon's egg. *Operation:* Extirpation of the tumour in the neck. *Microscopic examination U. 2879/37* (Prof. Fåhræus): The lymph node, which is the size of a chestnut, contains very little lymphatic tissue. By far the greater part of it consists of innumerable rounded masses of epithelioid cells. In some of these typical Langhans' giant cells may be found. Here and there a small amount of central necrosis may also be seen. Earlier a preparation such as this would certainly have been described as tuberculous but it is more probable that this is a case of *lymphogranuloma benignum.* This is suggested by the minimal degenerative changes and a certain tendency to fibrosis in the tuberculoid formations.

Case 5. ♂, born 1883. Treated as an out-patient in 1938 for pronounced swelling of the lymph nodes under the angles of the jaw. *On admission:* General condition unaffected. Blood showed no abnormality. *Operation:* Extirpation of the lymph nodes. *Microscopic examination U. 2524/38* (Prof. Gellerstedt): The lymph nodes are tightly packed with submiliary, sometimes confluent, epithelioid cell tubercles containing scanty foci of caseous necrosis and Langhans' giant cells. In several places the basic reticulum between the tubercles is sclerosed. The picture is similar to that seen in Schaumann's disease. Has the patient any of the other symptoms of this illness? *Patho-anatomical diagnosis:* Atypical tuberculosis.

Case 6. ♂, born 1904. Treated in a mental hospital 1931–39 under the diagnosis of imbecility. As far as the physical aspect of his condition is concerned, there were, in 1915, some old scars on the corneae and the hearing was impaired in the right ear. In 1916 there was an acute affection of the lungs with fever and cough which passed off after about a month. (There appears to have been no radiograph.) Examination in 1931 showed no somatic abnormality. *SR* (1934): 6 mm/hr. *WR:* negative. In 1935 it is noted that the patient had suffered since childhood from recurrent keratoconjunctivitis which had impaired the vision in both eyes. In Oct. 1934 an ophthalmologist was consulted on account of a fresh infiltration. After treatment the patient improved and by the spring of 1935 was almost symptom-free. *Tuberculin test:* Positive for 0.01 mg. *SR:* 8 mm/hr. 1938: There has been swelling of the lymph nodes of the neck for the last two months. *On examination:– Superficial lymph nodes:* There are hard, well-defined nodes on either side of the neck under the mandible and along the sternocleidomastoid. They are not tender and range up to the size of a pigeon's egg. *Abdomen:* The spleen is clearly palpable on breathing. *Diagnosis:* Sternberg's disease? *SR:* 16 mm/hr.

Blood: Monocytosis 14 %. *X-ray of lungs:* No abnormality. *X-ray of bones of hands:* No sign of l. b. *Microscopic examination U. 2899/38* (Prof. Gellerstedt): The whole lymph node is more or less uniformly infiltrated with small epithelioid cell tubercles of fairly uniform size, or with conglomerations of such tubercles showing central fibrosis. Only occasional Langhans' giant cells are to be seen. Foci of caseous necrosis are, however, but small and sparse in the larger conglomerates. The basal reticulum of the lymphoid tissue between the tubercles also shows a certain tendency to sclerosis. The changes in the lymph node are undoubtedly somewhat reminiscent of those seen in Schaumann's disease. It may therefore be asked whether other features of the syndrome are to be found in the patient. *Patho-anatomical diagnosis:* Atypical tuberculosis. There is a *final summary* in the notes dated 1938 saying: "The changes in the lymph nodes were suggestive of Schaumann's disease. The patient has shown the picture of uveoparotid fever[1] with severe keratoconjunctivitis sicca. The nodes in his neck have diminished in size and so has the spleen. The subjective symptoms have regressed. Radiography has shown no changes in the lungs or bones characteristic of Schaumann's diesase, but, since neither these nor skin lesions are essential parts of the syndrome we may consider the diagnosis of lymphogranulomatosis benigna as definite."

Case 7. ♀, born 1870. Received treatment in hospital in 1938 under the diagnosis of swelling of the neck. She had noticed a lump under the angle of the jaw on the right side for the previous 3 years. It altered in size somewhat from time to time and was sometimes somewhat tender. *On admission:* General condition good. *Local condition:* A tumour about the size of a small chestnut was felt below and in front of the angle of the jaw on the right side. It was rounded, freely moveable and had a smooth surface. Its consistency was firm and there was no tenderness. *Operation:* Extirpation of the mass. It was easy to remove. There were no adhesions to the surrounding structures. Cut surface greyish yellow, fairly firm. No liquefaction. *Microscopic examination U. 3711/38* (Prof. Gellerstedt): The whole lymph node is tightly packed with small, uniform, submiliary epithelioid cell tubercles which only occasionally show obvious necrosis; hardly any giant cells. Tendency to sclerotic induration around and between the tubercles. Apart from the very small amount of caseous necrosis the picture of the lymph node is typical of Schaumann's disease. *Patho-anatomical diagnosis:* Atypical tuberculosis.

Case 8. ♂, born 1875. Treated in hospital in 1939 with a diagnosis of lymphoma colli. Complained of one large and one small lump in the neck. *On admission:* General condition good. *Local condition:* Above the right shoulder there was a rounded, relatively soft, painless mass about the size of a goose egg (lipoma?). Behind the sternocleidomastoid muscle there was another mass about the size of an almond, painless and somewhat firmer though freely moveable relative to the skin and underlying tissues. *Operation:* Extirpation of the smaller tumour. *Microscopic examination V. 68/39* (I. Behring, M.D.): The lymph node is full of very closely packed foci of large, pale, epithelioid cells forming rounded circumscribed areas. There are, however, no peripheral walls of lymphocytes, nor do the foci show any tendency to necrosis. Giant cells are to be seen here and there, they are often of the Langhans type but sometimes look more like those associated with foreign body lesions. The lymph node thus contains tuberculoid granulation tissue of the type seen in *lymphogranuloma benignum* (Boeck's sarcoid), that is, groups of epithelioid cells without necrosis or a surrounding lymphocyte barrier.

Case 9. ♂, born 1906. Treated in hospital in 1939 under the diagnosis of tuberculous lymphoma + epilepsy. Father died of pulmonary tuberculosis. A niece suffers from pulmonary tuberculosis. Has had enlarged lymph nodes in the sides

[1] The daily notes contain no justification for this diagnosis.

and back of the neck for many years. During the past year they have grown larger, especially on the left side. *On examination:— Superficial lymph nodes:* There is a tender node the size of an almond behind the left angle of the jaw, also several small nodes on the left side of the neck. *X-ray of lungs:* Large hili with increased markings both upwards and downwards, especially on the right (Fig. 1). *Operation:* Removal of two lymph nodes which were well demarcated from the parotid and from one another. *Microscopic examination U. 815/39* (Prof. Gellerstedt): Histologically an atypical tuberculosis in that the whole node is infiltrated more or less densely with small epithelioid tubercles of similar size with only occasional giant cells and very scanty small foci of caseous necrosis, and, finally, a certain tendency to induration in many of the tubercles. — Are there any other signs of Schaumann's disease? *Patho-anatomical diagnosis:* Atypical tuberculosis. — *WBC:* 5,300/mm³. Eosinophils 6 %.

Case 10. ♀, born 1886. No heredity for tuberculosis. Treated in hospital in 1939 with the diagnosis of tuberculosis of the left parotid gland and regional lymph nodes + pernicious anaemia. She had had a swelling below the left ear since Oct. 1938 which had enlarged recently. It had also become somewhat tender and she had felt pricking and aching in it sometimes. No cough. Good appetite. No loss of weight. *On admission:* General condition good. *Throat:* No abnormality. *Lymphatic system:* A sausage-shaped mass as thick as a thumb extending from the lobe of the left ear about 7 cm downwards into the neck behind the jaw. It was fairly soft and freely mobile relative to both the skin and underlying tissues. Slightly tender, especially in the lower part. No other nodes were palpable in the neck, supraclavicular fossae, axillae or groins. *Operation:* Removal of the tumour. It was well separated from the surrounding structures except above where it was intimately adherent to the lower pole of the parotid gland. The tumour broke during its removal and was found to be homogeneous and rather brittle. *Microscopic examination U. 1140/39* (Prof. Gellerstedt): The larger fragment consists of a part of the parotid gland which is thickly infiltrated with miliary and submiliary tubercles forming isolated round foci or sometimes small agglomerates. Langhans' giant cells are fairly profusely distributed and several of them contain curious (calcified?) concentrically laminated bodies very like those found in the granulomatous foci of Schaumann's diesase. The tuberculous formations seen in the accompanying enlarged lymph nodes are, in principle, of the same type. Two acid- fast rods have been demonstrated in the middle of the very scanty caseous necrotic areas found in the centres of some of the tubercles. The picture as a whole is very reminiscent of that seen in the lymph nodes in Schaumann's disease, although there is no marked sclerosis of the basic reticulum or of the tubercles. It is also reminiscent of the changes in the parotid gland in uveoparotitis. *Patho-anatomical diagnosis:* Tuberculosis of the parotid gland and regional lymph nodes. *E.N.T. examination:— Nasopharynx:* No abnormality. *Nose:* Mild rhinitis with crust formation. *Tonsils:* Some adhesions and clots. The lymph nodes at the angle of the jaw would not appear to be associated with any lesion of the nose or throat. *X-ray of lungs:* No abnormality. *WBC:* 4,900/mm³. Eosinophils 7 %. *SR:* 13 mm/hr.

Case 11. ♀, born 1926. No heredity for, or known contact with, tuberculosis. Attended hospital in 1939 on account of a swelling under the left mandible. No pain or tenderness. *Operation:* Extirpation. *Microscopic examination U. 2666/39* (Prof. Gellerstedt): The enlarged lymph node is tightly packed with submiliary and miliary tubercles. There is only the slightest tendency to necrosis and the formation of giant cells in spite of the very large amount of granulation tissue. There is, however, a pronounced tendency to fibrosclerotic induration in the larger foci. Reminiscent of the appearance of lymph nodes in Schaumann's disease. Are there any other symptoms of this condition? *Patho-anatomical diagnosis:* Atypical tuberculosis.

Case 12. ♀, born 1909. Treated in hospital in 1939. Brother died of pulmonary tuberculosis. Previously always in good health. Never had erythema nodosum or pleurisy. Noticed a lump in the left axilla for the last half year which never gave any trouble. *On admission:* General condition good. *Lymphatic system:* In the left axilla there was a group of lymph nodes about the size of a walnut, matted together but not adherent to the surrounding structures. *Operation:* Extirpation of the axillary lymph nodes. *Microscopic examination U. 2728/39* (Prof. Gellerstedt): The nodes are tightly packed with fairly uniform submiliary tubercles, sometimes agglomerated in small groups. Very slight tendency to necrosis, only seen in the largest foci, but a considerable amount of fibrous induration is fairly widespread. On the other hand, there is a large number of giant cells, though they are not quite of the classical Langhan's type. The changes in the lymph nodes approach those seen in Schaumann's disease. Are the other symptoms of this syndrome present? — *SR:* 6 mm/hr. *Pirquet's reaction:* Positive. *X-ray of lungs:* Small calcified foci scattered over the hilar regions and the right lung field. No sign of active lesions in the parenchyma of the lungs or the pleurae.

Case 13. ♀, born 1922. Treated in hospital several times 1938–41 with the diagnosis hemosiderosis of the lungs (?) and lymphogranulomatosis benigna (?). One sister and two cousins dead of pulmonary tuberculosis. The patient had "glands in the neck" in 1926. These softened and formed fistulae. Treatment by scraping and X-rays. *On admission* (1938): General condition fairly good. *Superficial lymph nodes:* One firm node the size of a pea in the left supraclavicular fossa. Two the size of grains of corn at the angle of the jaw on the right side. *Abdomen:* No masses felt. *SR:* 12–37 mm/hr. *RBC* 2.3 mil/mm³. *WBC* 4,800–8,400/mm³. *Differential count:* 1 % eosinophils, 2 % monocytes. *X-ray of lungs:* A fuzziness over the greater part of the lung fields which is due, at least in part, to small flecks of shadow. Slight thickening of the pleura with an interlober line on the right side. The nature of the lesion cannot be determined. — *Pirquet's reaction:* Positive. Cultivation on Loewenstein's medium and a guinea pig test carried out with gastric lavage fluid gave negative results. Treated with iron with good effects. — When treated in 1939 and 1940 there were still nodes in the neck, some as large as beans. *X-ray of lungs* (1939): Little change since 1938. *X-ray of spine:* Tuberculous nodes to the right of the spine. *X-ray of lungs* (1940): General picture unchanged, though there is a paratracheal shadow above the right hilus. In 1940 more lymph nodes in the neck had become enlarged. Enlargement of the spleen? *X-ray of bones of hands and feet* showed no change. *Ophthalmological examination:* No pathological condition. — On account of the indeterminate nature of the lesions in the lungs an occipital lymph node was removed in 1940. *Microscopic examination U. 730/40* (Prof. Fåhræus): The somewhat enlarged lymph node contains a large number of tubercle-like groups of epithelioid cells which are largely fibrotic. It would appear that the individual tubercles are all of more or less the same age and, as no caseous necrosis or giant cells are to be seen, the picture is very like that seen in Schaumann's disease. *Patho-anatomical diagnosis:* Atypical tuberculosis. — During 1940 and 1941 the patient had repeated small hemoptyses, she developed cough and breathlessness and her condition deteriorated steadily till she died in 1941. *Autopsy* (U. 158/41) revealed that the lung condition was the anemia-producing form of so-called brown induration.

Case 14. ♂, born 1922. Treated in hospital in 1940 under the diagnosis tuberculous lymphadenitis? lymphogranuloma benignum? One sister and one brother dead of tuberculosis. In 1938 he had tuberculous nodes on the left side of his neck. For the past 1–1½ years he has again had enlarged nodes on the left side of his neck. They have grown larger during the last few months. Not tender. *On admission:* General condition good. *Lymphatic system:* A painless, fairly soft lymph node the size of a plum can be felt below the jaw on the left side. On the same

side there was a similar node, larger than a plum behind the angle of the jaw, and another just above it below the ear. On the left side of the back of the neck there was a soft lymph node the size of a date. *Operation:* Removal of all the nodes described. They were firm with no sign of liquefaction. *Microscopic examination U. 1732/40* (Prof. Gellerstedt): The abnormality consists of an astonishingly close and uniform distribution of epithelioid cell tubercles with only occasional traces of caseation and very sparse giant cells. No marked fibrosis, but there is much in the histological picture to suggest Schaumann's disease. Does the patient present any other signs of this complaint? *Patho-anatomical diagnosis:* Atypical tuberculosis. *WR:* neg. *SR:* 13 mm/hr. *X-ray of lungs* (1938): In both hilar regions there are several calcified nodes about the size of small peas. No sign of any active lesion of the lungs. Sinus and diaphragm normal. *X-ray of lungs* (1940): No active lesions. *X-ray of bones of hands and feet:* No abnormality.

Case 15. ♂, born 1905. Treated in hospital in 1941 under the diagnosis tuberculous lymphoma of the neck. No family history of tuberculosis. Had a swelling on the right side of the neck since childhood. It had not grown much and had given no trouble apart from swelling up when the patient "caught cold". *On admission:* General condition good. *Superficial lymph nodes:* No enlargement. *Local condition:* A round tumour on the right side of the neck about the size of a walnut and nearly as hard as cartilage. No tenderness. The tumour was freely mobile. The overlying skin could be lifted and was found to be unaffected. *Preoperative diagnosis:* Branchial cyst. *Operation:* Extirpation. *Microscopic examination U. 136/41* (Prof. Fåhræus): The enlarged lymph nodes are absolutely crammed with epithelioid cell tubercles some of which contain giant cells and here and there definite caseous necroses. If these were not present the histological picture would be that of lymphogranuloma benignum. *Patho-anatomical diagnosis:* Atypical tuberculosis. — *X-ray of lungs:* Marked emphysema without signs of active tuberculosis. *SR:* 5 mm/hr. *WBC:* 9,700/mm³.

Case 16. ♂, born 1908. Treated as an out-patient in 1941. No heredity for tuberculosis. For 3–4 years had had a small tumour under the mandible on the left side of the neck just in front of the angle of the jaw. It had scarcely increased in size. *Operation:* Extirpation. At operation two tumours were found. They were fairly easy to shell out and had smooth even surfaces and were of soft, rather brittle consistency. *Microscopic examination U. 236/41* (Prof. Fåhræus): The two greatly enlarged lymph nodes are tightly crammed with small masses of epithelioid cells, in some places there are giant cells and the beginnings of caseous necroses. The large number of the tubercles, their uniform appearance, the presence of a tendency to fibrosis and the small amount of caseous change combine to form a picture like that seen in lymphogranuloma benignum. *Patho-anatomical diagnosis:* Atypical tuberculosis.

Case 17. ♀, born 1898. Treated in hospital in 1941 under the diagnosis lymphogranulomatosis benigna. No heredity for, or known contact with, tuberculosis. In 1934 dry pleurisy. Tonsils removed in the same year for sore throat. In the spring of 1938 complained of increasing tiredness, loss of weight and shortness of breath. At about the same time the patient noticed a swelling on the right side of her neck below the jaw and just in front of the sternocleidomastoid. In 1940 a new tumour was noticed more laterally in the neck. *On admission:* General condition good. *Local condition:* Three well-defined, painless, semi-mobile, tumours about the size of hazel nuts can be felt along the anterior border of the sternocleidomastoid on the right side of the neck. The overlying skin is freely mobile. More laterally in the neck there is a similar but softer tumour. *WBC:* 6,800/mm³. *Differential count:* Eosinophils 1.5 %, monocytes 8 %. *Pirquet's reaction:* Positive. *SR:* 6 mm/hr. *Operation:* Extirpation of a lymph node. *Preoperative diagnosis:*

Tuberculosis? Sternberg's disease? *Microscopic examination U. 984/41* (Prof. Fåhræus: The lymph node is absolutely packed with small, sometimes confluent, tubercles which all appear to be of the same age. No giant cells are to be seen. Central caseous necrosis is present but only to a very slight extent. The picture is like that seen in lymphogranuloma benignum. *Patho-anatomical diagnosis:* Atypical tuberculosis. — *X-ray of lungs:* The left lateral part of the diaphragm is fixed. Minimal thickening of the pleura over the left apex. No active lesion of the parenchyma visible. No enlargement of the mediastinal shadow.

Case 18. ♂, born 1927. Treated in hospital in 1941 under the diagnosis lymphadenitis of the neck. Mother had tuberculosis. The patient had had a lump on the left side of his neck for almost as long as he could remember. Every winter it used to swell. It was sometimes a little tender but there was no reddening of the skin. *On admission:* General condition good. *Local condition:* Under the angle of the jaw on the left side there was a firm, painless, completely mobile tumour about the size of a plum and slightly lobulated on the surface. A similar tumour about the size of a hazel nut was found in the right side of the neck and another of the same size in the right axilla. Two similar tumours were felt in the left axilla. — *Operation:* Extirpation of the tumour in the left side of the neck. *Microscopic examination U. 1008/41* (Prof. Fåhræus): The lymph node is thickly studded with small new tubercles, sometimes confluent. They are mostly epithelioid cell tubercles, but giant cells are also present as are numerous, though small, areas of caseous necrosis. *Patho-anatomical diagnosis:* Atypical tuberculosis. *X-rays of lungs*: No abnormality. *Pirquet's reaction:* Positive.

Case 19. ♂, born 1922. Treated as an out-patient in 1941. He had an enlarged node under the jaw for several years. It had not changed during recent years. *On admission:* Good general condition. *Lymphatic system:* Under the jaw on the right side there was a flat, well defined, fairly firm tumour about 2 cm in diameter. *Operation:* Extirpation of a lymph node the size of an almond from under the jaw. *Microscopic examination U. 1615/41* (Prof. Gellerstedt): A lymph node thickly studded with mostly submiliary tubercles with only the slightest tendency to caseous necrosis and very few giant cells but without any great tendency to fibrosis. It is thus, in some respects, reminiscent of the tuberculosis of the lymph nodes commonly seen in Schaumann's disease. *Patho-anatomical diagnosis:* Atypical(?) tuberculosis.

Case 20. ♂, born 1919. Treated in hospital in 1941 under the diagnosis tuberculous lymphoma of the neck. No family history of, or known contact with, tuberculosis. During his military service in 1941 the patient noticed two nodes on the right side of his neck. These have since swollen up from time to time. They are at present swollen and tender and cause difficulty in chewing. *On admission:* General condition good. *Lymphatic system:* Two small rather tender lymph nodes barely the size of hazel nuts may be felt behind the angle of the jaw on the right side. They are somewhat adherent to the surrounding structures. *Pirquet's reaction:* Positive. *SR:* 4 mm/hr. *Operation:* Extirpation. *Microscopic examination U. 3909/41* (Prof. Fåhræus): Three of the four lymph nodes have been sectioned. They all present the same picture. The lymphatic parenchyma is completely filled with uniform-sized groups of epithelioid cells. In and around these there is a pronounced connective tissue reaction. No giant cells. Caseous necrosis is present only very exceptionally. The picture is consequently that seen in *lymphogranuloma benignum.*

Case 21. ♀, born 1892. Under care in a sanatorium in 1932 for pulmonary tuberculosis. Treated in hospital in 1943 for a swelling under the left side of the lower jaw. Noticed it about a year ago. *On admission:* General condition good. *Lymphatic system:* There is a swelling the size of a walnut beneath the left

ramus of the mandible. *Operation:* It was impossible to determine whether the tumour was a lymph node or an aberrant salivary gland. *Preoperative diagnosis:* Malignant tumour? *Microscopic examination U. 152/43* (Prof. Fåhræus): The markedly enlarged lymph node is tightly packed with tubercles. These would seem to be of two different crops, i.e., there is a certain number of fibrotic tubercles, though the great majority are quite recent. Some of the tubercles show caseous necroses. Apart from this the picture shows a certain similarity to that seen in the lymph nodes in Schaumann's disease. *Patho-anatomical diagnosis:* Atypical tuberculosis. *SR:* 61 mm/hr. *Tubercle bacilli in sputum:* Absent. *X-ray of lungs:* In the right apex above the second rib there is a streaky and mottled opacity against which several rounded areas of decreased density—bronchiectases—stand out. In the lower part of the opacity there is a clear area barely the size of the tip of a thumb with a distinct arched upper border. The trachea is convex towards the right at the level of the opacity.

Case 22. ♀, born 1913. Treated as an out-patient in 1943. No family history of tuberculosis. Has had a little lump behind the left ear for a long time. This has grown somewhat recently and is tender. *Operation:* Extirpation of the tumour. *Microscopic examination U. 1282/43* (Prof. Gellerstedt): Corresponds with the appearance of the lymph nodes seen in Schaumann's diesase. Submiliary type, pronounced fibro-reticular induration, no necrosis, giant cells few and atypical. *Patho-anatomical diagnosis:* Atypical tuberculosis.

Case 23. ♂, born 1926. Treated as an out-patient in hospital in 1943. No heredity for tuberculosis. For about the last five years has had a slowly growing nodule in the left cheek. *On admission:* General condition satisfactory. *Lymphatic system:* In the soft tissues of the left cheek, above the middle of the ramus of the mandible, a soft, elastic, somewhat flattened, freely mobile tumour about the size of a hazel nut may be felt. *Operation:* Extirpation of the tumour. It was soft and elastic and the cut surface was greasy. *Microscopic examination U. 1927/43* (Prof. Gellerstedt): The histological picture corresponds exactly with that seen in Schaumann's disease. *Patho-anatomical diagnosis:* Atypical tuberculosis. *X-ray of lungs:* No changes. *Mantoux:* 0.01 mg positive.

Case 24. ♂, born 1894. Treated as an out-patient in 1943. No heredity for tuberculosis. Had had a painless tumour in the right supraclavicular fossa for one and a half years. It was found to be the size of a grape, very mobile and rounded. A similar rather larger mass had been present in the submental region since the patient was 20 years old. *Operation:* Extirpation of the tumour from the supraclavicular fossa. *Microscopic examination U.2295/43* (Prof. Gellerstedt): An unusual form of close diffuse infiltration with usually confluent, submiliary, obviously recent tubercles. Only very occasional necroses and very scanty giant cells are present. A certain amount of (early?) sclerosis of the basic reticulum between the tubercles. It is possible that this is an early case of Schaumann's disease. *Patho-anatomical diagnosis:* Tuberculosis (incipient Schaumann's disease?).

Case 25. ♀, born 1900. Treated in hospital in 1943. One brother dead of tuberculosis in 1929. The patient had pleurisy 14 years ago. Has noticed increasing swelling under both sides of the lower jaw for the past 10–12 years. This has never caused any trouble. Had X-ray treatment 5 years ago which caused the swelling to subside for a time. Desired an operation for cosmetic reasons. *On admission:* General condition good. *Throat:* No abnormality. *Lymphatic system:* In positions corresponding to those occupied by the submaxillary salivary glands there are swellings the size of pigeon's eggs. They are quite hard, painless and freely moveable relative to the skin and underlying tissues. No other enlarged nodes palpable. *Operation:* Extirpation. On the left side a double mass the size of two chestnuts

was removed and on the right two separate masses each rather larger than a chestnut. They were rounded, well defined and lymph-node-like. *Microscopic examination U. 2459/43* (Prof. Gellerstedt): Three enlarged lymph nodes densely infiltrated with submiliary epithelioid cell tubercles diffusely arranged. Only isolated giant cells. Many but very small caseous necroses in the tubercles. A certain tendency to induration of the basic reticulum in several places. The chronic and benign course of the lesion suggests Schaumann's disease. The histological picture also corresponds in many respects with that seen in this condition. *Patho-anatomical diagnosis:* Tuberculosis (Schaumann's disease?). *SR:* 9 mm/hr. *WBC*: 5,100/mm³. *Differential count:* Eosinophils 2 %, monocytes 13 %.

Case 26. ♀, born 1889. Treated in a sanatorium in 1944 under the diagnosis of Schaumann's disease and afterwards as an out-patient at the central dispensary. No family history of tuberculosis. Never had erythema nodosum, pleurisy or glands in the neck. Changes suggestive of Schaumann's disease were seen when the lungs were screened in June 1944. The radiograph of the lungs which was then taken showed definite broadening of the hilar areas on both sides, as well as flecks of opacity in the parenchyma of both sides. Etiology unknown. Schaumann's disease? — *Mantoux:* 1 mg negative, 3 mg positive (11 × 14 mm). Extirpation of a lymph node from the left groin. *Microscopic examination V. 2683/44* (I. Behring, M.D.): The lymph node shows a profuse scattering of epithelioid cell foci without any tendency to caseous necrosis. The picture corresponds very well with that seen in Schaumann's disease. *Patho-anatomical diagnosis:* Schaumann's disease. — *X-ray of lungs* (1945): Picture unchanged. It was noted in 1946 that the patient became breathless on very slight exertion. *X-ray of lungs:* There is a fairly general increase in the markings in both lung fields. Both hilar shadows are somewhat enlarged and deformed. In the left hilus there are widespread areas of calcification grouped in rings (Fig. 2). The picture may be considered to correspond with that of Schaumann's disease but the calcified areas in the left hilus are remarkable. *SR:* 24 mm/hr. *X-ray follow-up* (in Dec. 1946): Condition of the lungs unchanged. *SR:* 30 mm/hr.

Case 27. ♂, born 1913. Treated as an out-patient in 1944. No heredity for tuberculosis. Had had a tumour in the neck since 1940. *Operation:* Extirpation. *Microscopic examination U. 3142/44* (Prof. J. Mellgren): The lymph node is the size of an almond and is tightly packed with rounded foci of epithelioid cells which are often separated from one another by narrow strips of hyaline connective tissue. A minimal amount of caseation in one or two places. No giant cells. The picture thus corresponds in all important respects with that seen in Schaumann's disease. *Patho-anatomical diagnosis:* Atypical tuberculosis.

Case 28. ♀, born 1893. Treated in hospital in 1939 for non-toxic goitre + hypertension and in 1944 for lymphadenitis of the neck. No heredity for tuberculosis. Had had a nodule in the left side of the neck for some time. *Throat:* No abnormality. *Lymphatic system:* A rounded, fairly hard, freely mobile tumour nearly the size of a plum can be felt on the left side of the neck. *Operation:* Extirpation. *Microscopic examination U. 4863/44* (Prof. Gellerstedt): Both lymph nodes are tightly packed with epithelioid cell tubercles. Giant cells are very sparse. Caseous necrosis is only seen as traces in occasional tubercles. There is a striking tendency to sclerosis of the basic reticulum of the tubercles. The picture is thus very like that seen in the lymph nodes in Schaumann's disease. The foreign bodies in the giant cells which are often seen in that condition are however absent. *Patho-anatomical diagnosis:* Atypical tuberculosis.

Case 29. ♀, born 1886. Treated in hospital in 1945 for chronic myocarditis. No heredity for tuberculosis. In about 1900 the patient noticed a hard painless tumour

growing slowly in the region of the right parotid gland (salivary gland tumour?). During examination in connection with treatment for the cardiac condition it was noticed that the position of the right parotid gland was occupied by a firm tumour with a smooth surface which was freely mobile relative to the skin and underlying tissues. Immediately beneath this tumour there was a bundle of lymph nodes of the same consistency as the tumour and stretching along the lower border of the right side of the mandible as far as the midline. The nodes were freely mobile relative to the skin and underlying tissues but were hard to differentiate from one another. There were also two lymph nodes behind the sternocleidomastoid, one the size of an almond and the other the size of a bean. No tenderness. *Operation:* Extirpation. *Microscopic examination U. 1052/45* (Prof. Gellerstedt): Atypical tuberculosis presenting a microscopical appearance which corresponds fairly well with the changes in the lymph nodes seen in Schaumann's disease. Even the characteristic foreign bodies in the giant cells are present. *Patho-anatomical diagnosis:* Schaumann's disease? *Pirquet's reaction:* Positive. *WBC:* 4,400/mm³. Eosinophils 2%, monocytes 4%. No clinical signs of lymphogranulomatosis benigna apart from the enlargement of the lymph nodes. *Final note:* "The lymph nodes in the neck presented the microscopic picture of Schaumann's disease, but the patient is Pirquet positive and furthermore the nodes have been present for several years."

Case 30. ♀, born 1885. Treated in hospital in 1945 for toxic goitre. No heredity for tuberculosis. *Operation:* Bilateral subtotal thyroidectomy and exstirpation of lymph nodes. *Microscopic examination U. 2635/45* (Prof. Gellerstedt): The lymph nodes show the picture of a dense formation of submiliary tubercles clustered together in groups. There is little caseous necrosis and few giant cells. A certain amount of fibrosis in some places in the basic reticulum within and between the tubercles. Curious concentrically laminated structures such as are quite common in the giant cells in Schaumann's disease may occasionally be seen. The picture suggests the presence of this condition. *Patho-anatomical diagnosis:* Atypical tuberculosis.

Case 31. ♂, born 1907. No heredity for tuberculosis. Became tired in the winter 1944–45. In April 1945 there was an enlargement of the lymph nodes in the left axilla which became more marked after an infection of the hand. Was examined at a central dispensary in May 1945. The *Mantoux* was then "weakly positive". Several smooth, painless, well-defined lymph nodes, none larger than a walnut, were felt in the left axilla. There was no sign of periadenitis. *WBC:* 7,800/mm³. *X-ray of lungs:* No abnormality. The dispensary physician thought that the case was probably not one of tuberculosis and sent the patient to hospital for exstirpation of one of the lymph nodes. *Microscopic examination U. 3755/45* (Prof. Gellerstedt): The whole lymph node is thickly infiltrated with submiliary tubercles with a definite tendency to induration; insignificant amounts of caseation and rudimentary formation of giant cells. Corresponds histologically with the changes seen in Schaumann's disease. *Patho-anatomical diagnosis:* Atypical tuberculosis. In 1950 hemoptysis. *Sputum examinations:* No tubercle bacilli found. *X-ray of lungs:* Bilateral streaky and finely flecked opacities mostly in the first and second interspaces. The picture is more like that seen in Schaumann's disease than anything else. — Sanatorium treatment was suggested and the patient was admitted in Oct. 1950. At that time his tuberculin reaction was negative for 1 mg. There was marked enlargement of the heart. It was thought that the hemoptysis had been due to infarction or oedema of the lungs. In Nov. 1950 there were epigastric pains. Thrombosis of the mesenteric veins was suspected. Laparotomy was performed and the diagnosis was confirmed. The patient died. No autopsy was performed.

Case 32. ♀, born 1895. Treated in hospital in 1947–48 for tuberculosis of the ascending colon and lymphadenitis of the left axilla. No family history of tuber-

culosis. Had had a swelling in the right armpit for the past two years. It had not grown larger recently and had never been tender. About half a year ago she had abdominal trouble with attacks of pain every 3 or 4 weeks. *On admission:* General condition good. *Local condition:* In the depths of the right axilla a soft, rounded, well-defined lymph node was felt. It was about the size of a walnut and not tender. *Operation:* Extirpation: The node was deeply situated and well defined. The cut surface was greasy. *Microscopic examination U. 77/48* (Prof. Gellerstedt): The picture is that of somewhat atypical tuberculosis in that there is no caseous necrosis but a uniform, densely grouped formation of submiliary tubercles without giant cells. It is thus somewhat reminiscent of the changes seen in the lymph nodes in Schaumann's disease, although the tendency to induration is not very conspicuous. *Patho-anatomical diagnosis:* Atypical tuberculosis. *X-ray of lungs:* A couple of small calcified nodes in the left hilus, otherwise no abnormality. — As the patient was suffering from abdominal trouble the colon was X-rayed and an infiltrative and stenosing process was found in the ascending part. A neoplasm was diagnosed and a laparotomy performed. *Operation:* Resection of the caecum and ascending colon. At operation a scarred stricture and a deep ulcer were found in the neighbourhood of the valve of Bauhin. *Patho-anatomical diagnosis* (*U. 352/48*): Tuberculosis.

Case 33. ♂, born 1881. Treated in hospital in 1948. No family history of tuberculosis. Tuberculous lymph nodes of the neck in 1944. Had noticed a couple of nodes in the neck for the past eighteen months. *On admission:* General condition good. *Local condition:* In front of the right ear there was a soft, mobile lymph node the size of a hazel nut. Lower down in the neck in front of the sternocleidomastoid there was a similar node the size of a plum. *Operation:* Extirpation. The smaller upper lymph node was adherent to the parotid gland and very difficult to separate. No softening. The other was easier to separate. *Microscopic examination S. 2144/48* (F. Wahlgren, M.D.): The whole of the lymph node is thickly studded with rounded tubercle-like groups of epithelioid cells which often coalesce to form larger masses. Occasional giant cells are to be seen. Small caseous necroses may also be observed here and there and there is some tendency to fibrous induration. Tubercle bacilli were not demonstrated in the section. *Patho-anatomical diagnosis:* Probably lymphogranuloma benignum.

Case 34. ♂, born 1938. Treated in hospital in 1948 for cholesteatoma of the middle ear and healed pulmonary tuberculosis (primary comlex). Previously (at the age of about two) treated in a sanatorium for tuberculosis of the lungs, probably a primary complex localised to the lungs and hilar lymph nodes. *X-ray of lungs* (1948): Calcified primary complex in the left lung. The hilar regions are somewhat fibrosed. An irregular calcified paratracheal node the size of a haricot on the left side. *Operation:* Extirpation of a lymph node. *Microscopic examination U. 3167/48* (Prof. Gellerstedt): Scattered groups of submiliary tubercles without necroses or conspicuous giant cells. This may well be a case of Schaumann's disease. *Patho-anatomical diagnosis:* Atypical tuberculosis. — Re-examination of the X-ray pictures of the lungs taken in 1948 shows no changes characteristic of Schaumann's disease. There are, however, numerous enlarged lymph nodes, both in the hilar regions and paratracheally.

Case 35. ♂, born 1913. Treated in hospital in 1948. No family history of, or known contact with, tuberculosis. Had an enlarged node in the neck for at least 20 years. New nodes have appeared in the left supraclavicular fossa during the past few months. These are adherent to one another and have gradually formed a mass of firm, smooth, freely mobile, enlarged nodes the size of a fist. No other noteworthy abnormalities were found. Extirpation of the lymph nodes. *Microscopic examination U. 3754/48* (Prof. Fåhræus): The material consists of four

lymph nodes the size of prunes well separated from one another. Microscopically they are seen to be packed as tightly as possible with tubercles of uniform size. Some of these contain giant cells. Several show the beginnings of caseous necrosis. This may possibly be a case of Schaumann's disease but the presence of caseation is perhaps more indicative of tuberculosis. *Patho-anatomical diagnosis:* Atypical tuberculosis. *X-ray of the lungs:* Several small apical pleural thickenings and a thin interlobar line on the right side. *SR:* 2 mm/hr.

Case 36. ♂, born 1903. The patient's mother suffered from tuberculosis. Had a painless lump the size of a walnut on each side of the neck for the past few months. Felt well. *SR:* 8 mm/hr. *Operation:* Extirpation of the two lymph-node-like swellings. *Microscopic examination U. 5489/48* (Prof. Gellerstedt): Submiliary tubercles closely clustered together in both lymph nodes. Only occasional giant cells and no definite caseous necrosis. Indurative changes in many places. The atypical picture corresponds with that seen in Schaumann's disease. Are any other symptoms of this condition present? *Patho-anatomical diagnosis:* Atypical tuberculosis. *X-ray of lungs:* No abnormality.

Case 37. ♀, born 1888. No heredity for tuberculosis. Operated in 1938 for Graves' disease. Returned in 1949 having recently noticed a swelling under the right ramus of the mandible where a couple of firm tumours the size of a plum could be felt. No other palpable masses or enlargement of lymph nodes. This was interpreted as a recurrence of her earlier condition in remaining parts of the thyroid gland. *Operation:* Extirpation. *Microscopic examination U. 1265/49* (S. Ranström, M.D.): A lymph node dotted with epithelioid cell tubercles containing giant cells. There are, however, no caseous necroses but small fibrinoid necroses and a marked tendency to induration. The picture corresponds with that in lymphogranulomatosis benigna. *Patho-anatomical diagnosis:* Atypical tuberculosis. *X-rays of lungs:* Very slight peribronchial induration on the right side but no other abnormality. *SR:* 49 mm/hr.

Case 38. ♀, born 1895. One brother had suffered from tuberculosis. Treated as an out-patient in 1949 for a swelling under the left angle of the jaw. It had been present for some years. *Operation:* Extirpation. *Microscopic examination S. 2189/49* (F. Wahlgren, M.D.): The enlarged lymph node is closely set throughout with tubercle-like groups of epithelioid cells some of which contain giant cells of the Langhans type. Some of these groups of epithelioid cells show the beginnings of central caseous necrosis but this is not at all well marked. Occasionally the Langhans cells contain laminated calcified bodies. Tubercle bacilli were not demonstrated in the section. The histological picture strongly suggests that it is a case of *lymphogranuloma benignum. Mantoux:* 0.05 mg positive. *SR:* 50 mm/hr. *X-ray of lungs:* The domes of the diaphragm bear a normal relation to each other and there is no pleural exudate. There is a calcified focus the size of a pea in the base of the right lung, another nearly as large as a hazel nut, as well as a smaller calcified focus in the right hilus. The hilar shadows are of normal contour. No other abnormalities to be seen in the parenchyma.

Case 39. ♀, born 1873. No heredity for tuberculosis. In the spring of 1949 the patient noticed a small tumour in the left side of the neck. Never tender. Slight rise of temperature. Went to hospital in June 1949. *On admission:* In the left lateral triangle of the neck there was a mobile tumour the size of a pigeon's egg. The overlying skin was not infiltrated. *Operation:* Extirpation of several lymph nodes rather adherent to one another. One was sent for biopsy. *Microscopic examination S. 2228/49* (F. Wahlgren, M.D.). The lymph node is tightly packed with tubercle-like groups of epithelioid cells containing giant cells of the Langhans type. One or two of these groups of epithelioid cells show the beginnings of

central caseous necrosis. The histological picture sugests that this is a case either of *tuberculosis or lymphogranuloma benignum, probably the latter.* Tubercle bacilli were not demonstrated in the section. *X-ray of lungs:* No changes in the lungs or hili such as are found in Schaumann's disease. *X-ray of bones of hands and feet:* Moderate osteoporosis. *Mantoux:* 0.05 mg positive.

Case 40. ♂, born 1925. Treated in hospital in 1949. Erythema nodosum in 1937. Had had a tumour behind the left angle of the jaw. It gradually increased in size since 1942 and varied in size from time to time. *On admission:* General condition good. *Throat:* Small pitted tonsils without any sign of inflammation. *Lymphatic system:* Behind the left angle of the jaw can be felt an oval, fairly well defined, rather soft tumour about the size of a pigeon's egg lying in the subcutis and not tender. No lymph node enlargement. *Operation:* Extirpation. The tumour gave the impression of being an aberrant parotid gland tumour. *Microscopic examination U. 4038/49* (Prof. Gellerstedt): Parts of a lymph node infiltrated with submiliary tubercles without caseous necrosis and with very few giant cells. Corresponds with the changes seen in Schaumann's disease. *Patho-anatomical diagnosis:* Atypical tuberculosis. *SR:* 2 mm/hr. *WBC:* 5,000/mm³. *Mantoux:* 0.1 mg positive.

Case 41. ♀, born 1928. Treated in hospital in 1950 for right-sided lymphadenitis of the neck. No family history of tuberculosis. Previously healthy. Had had catarrh of the throat for two weeks. Noticed a tender lump in the left side of the neck. *Operation:* Extirpation. *Microscopic examination V. 2109/50* (I. Behring, M.D.): The lymph node is closely packed with groups of epithelioid and giant cells. These formations show no marked perifocal reaction and no sign of caseous necrosis, although there is fibrosis and hyalinisation in several places. This is more probably Schaumann's disease than tuberculosis. *Patho-anatomical diagnosis:* Schaumann's disease? *X-ray of lungs:* No abnormality. *Mantoux:* Positive.

Case 42. ♂, born 1902. Treated as an out-patient in 1950 for lymphadenitis of the neck. Had been operated on at the age of 21 for left-sided tuberculosis of the kidney. Several cases of tuberculosis in the family. *Operation:* Extirpation of a lymph node of the neck. *Microscopic examination S. 2162/50* (F. Wahlgren, M.D.): The enlarged lymph node is densely and diffusely infiltrated with small irregularly rounded groups of epithelioid cells. Giant cells of the Langhans type are to be found in some of them. Isolated small necroses were also seen. The microscopic picture is typical of *lymphogranuloma benignum.* — *X-ray of lungs:* No noteworthy abnormality. *Mantoux:* 0.01 mg positive.

Case 43. ♀, born 1915. Treated in hospital in 1951. Had noticed a lump under the right angle of the jaw for about a year. The tumour might have got larger during the past year. It was not the least tender and had never suppurated. *On admission:* General condition good. *Local condition:* In the submandibular region on the right side there was a rounded, mobile, almost painless tumour. *Preoperative diagnosis:* Lymphadenitis or tumour of a salivary gland. *Operation:* Immediately below the margin of the lower jaw at the angle of the mandible there was a tumour the size of a walnut. It was rounded and quite smooth on the surface and had a well-defined capsule which made it easy to shell out. It was solid and had a light brown cut surface, relatively soft in consistency and with no areas of softening. Medial to this tumour there were three smaller ones, one the size of a pea and two the size of haricots. These were also removed. All of the tumours lay in the space above the submaxillary gland and appeared to have no connection with it. *Microscopic examination S. 2181/50* (O. Möller, M.D.): The material consists of some lymph nodes, the normal structure of which is completely destroyed and replaced by numerous epithelioid cell tubercles containing occasional giant cells of the

Langhans type. There is no disintegration of the tubercles and no tendency to coalesce, hence this is probably a case of *Schaumann's disease.* — *Re-examination* of the material under investigation (F. Wahlgren, M.D.) showed that there were a couple of old caseous necroses in the central part of one of the lymph nodes and that they were bounded by connective tissue of coarse structure containing few cells. The rest of the lymph node tissue is densely studded with groups of epithelioid cells and here the histological picture is undoubtedly that seen in Schaumann's disease. Although a careful search was made, no tubercle bacilli were demonstrated in the section. The histological picture cannot form the sole basis for the diagnosis in this case. It seems most probable to me that it is a question of tuberculosis, the patient having become tuberculin-negative in a later stage of the disease, and that the structure which looks like that seen in Schaumann's disease has arisen as a result of this. *SR:* 15 mm/hr. *X-ray of lungs:* No abnormality.

Case 44. ♂, born 1933. No family history of, or known contact with, tuberculosis. At the age of six he had a lymphoma of the hilus and was then under observation at a central dispensary. *X-ray of the lungs* showed considerable enlargement of the hilar shadows. There was, in particular, a well-defined focus in the left hilus. *Diagnosis:* Hilar tuberculosis, probably healing. — In 1950 he went to a hospital on account of enlarged lymph nodes of his neck which had been present for a couple of years. They gave no trouble. On investigation he was found to have a group of lymph nodes on the left side of the neck ranging up to the size of walnuts. The nodes were soft and well separated from the surrounding tissues without periadenitis. No other lymph nodes were palpable. *SR:* 4 mm/hr. *WBC:* 4,700/mm³. Eosinophils 2 %, monocytes 5 %. *Operation:* Extirpation of the lymph nodes. *Microscopic examination S. 2235/50* (F. Wahlgren, M.D.): The considerably enlarged lymph nodes are densely packed with irregularly rounded groups of epithelioid cells. These contain isolated giant cells of the Langhans type. In some places there are signs of the beginnings of fibrous induration. There are, however, no definite necroses. The histological picture makes it seem likely that this is a case of *lymphogranuloma benignum.* — *X-ray of lungs:* On the left side there are some streaky shadows and a cap of pleural thickening over the apex. The changes are certainly tuberculous in origin but seem to date from some time ago.

Case 45. ♀, born 1874. No heredity for tuberculosis. Had an enlarged lymph node in the neck for two years. *Operation:* Extirpation. *Microscopic examination V. 2325/50* (I. Behring, M.D.): The lymph node is nearly as large as a plum and is thickly studded all over with tubercle-like epithelioid-giant-cell foci without any sign of necrosis or perifocal reaction. The picture is more suggestive of Schaumann's disease than of tuberculosis. *Patho-anatomical diagnosis:* Schaumann's disease. *X-ray of lungs:* No abnormality.

Case 46. ♂, born 1918. Treated in hospital in 1950 for lymphogranulomatosis benigna. No family history of tuberculosis. Had asthma as a child, appendicectomy in 1942, tonsillectomy in 1927, and a generalised gangrenous skin disease in 1948. In October 1950 he had a sudden attack of vertigo and nausea and could not sit up. Slight, but not significant, discomfort in the neck but no real headache. No tinnitus. No impairment of vision. The dizziness lasted several hours. Nystagmus on looking to the left. For the previous 5–6 years he had noticed a swollen lymph node in the neck. Further nodes had appeared during the past 3–4 years. *On admission:* General condition satisfactory. No stiffness of the neck. *Superficial lymph nodes:* Diffuse enlargement of the lymph nodes on both sides high up under the sternocleidomastoid. Some the size of almonds were found below the left angle of the jaw, in the right supraclavicular fossa and in the left axilla. They were not tender and were soft and freely moveable. *Abdomen:* Liver, spleen and kidneys were

not palpable. *Nervous system:* Possible unsteadiness of gait, nystagmus on looking to the left. Otherwise no abnormality. *X-ray of lungs:* Diaphragmatic movements equal on both sides. Calcified primary complex in the left lung field with a little calcification in the parenchyma at the level of the first rib in front and some fibrous streaks in the upper part of the left hilus. No other lesions visible. Upper mediastinum of normal breadth. No radiological evidence of any active lesion. *Operation:* Excision of a lymph node. *Microscopic examination S. 3110/50* (F. Wahlgren, M.D.): The lymph node is about the size of a walnut and is tightly packed throughout with tubercle-like groups of epithelioid cells, in which there is sometimes a trace of caseous necrosis and sometimes the beginnings of fibrous induration. Giant cells of Langhans' type are to be seen here and there. The histological picture suggests that this is a case of *lymphogranuloma benignum.* — *Final note:* "The patient's vestibular trouble was soon relieved. Biopsy of a lymph node has shown a picture suggestive of lymphogranuloma benignum. His tuberculin reaction is positive with 0.1 mg, and the X-ray of his lungs negative. If Schaumann's disease is present it may account for the neurological symptoms as well as the enlarged lymph nodes."

Case 47. ♀, born 1915. Treated in hospital in 1950 for Schaumann's disease. No heredity for tuberculosis. Had had a painless tumour beneath the jaw for two or three years. This had grown larger recently. Admitted for operation. *On admission:* General condition good. *Local condition:* There is a well-defined lump the size of a chestnut beneath the jaw. It is mobile and not tender. *WBC:* 9,200/mm³. *SR:* 18 mm/hr. *Operation:* Extirpation. *Microscopic examination V. 3697/50* (I. Behring, M.D.): The lymph node is found to be tightly packed with foci of epithelioid cells without any noticeable surrounding barrier of lymphocytes. No necrosis but greater or lesser degrees of induration here and there. This picture is more suggestive of Schaumann's disease than of tuberculosis. *Patho-anatomical diagnosis:* Schaumann's disease. — Follow-up in a sanatorium showed that the patient was tuberculin-positive for 0.01 mg. *X-ray of lungs:* No abnormality. — No lesions of skin. — No palpable enlargement of lymph nodes.

Case 48. ♂, born 1903. No heredity for, or known contact with, tuberculosis. Treated as an out-patient in 1950 when he complained of a tumour the size of a hazel nut above the right sternoclavicular joint. The tumour was hard and painless and had been present for about a year. *Operation:* Extirpation of a firm lymph node the size of a haricot from loose surrounding tissues. *Microscopic examination U. 4687/50* (author): Almost the whole lymph node is studded with submiliary-miliary epithelioid cell tubercles with few giant cells. No caseous necrosis but 'fibrinoid' necrosis in places. The picture corresponds with that seen in lymphogranulomatosis benigna. *Patho-anatomical diagnosis:* Atypical tuberculosis. *SR:* 5 mm/hr. *WBC:* 4,900/mm³. Eosinophils 2 %, monocytes 4 %. — At follow-up the patient was found to have small nodes at both angles of the jaw. *X-ray of lungs:* No abnormality. *Mantoux:* 1.0 mg positive.

Case 49. ♀, born 1887. Treated in hospital in 1950 for a tumour of the abdomen. Her general condition had deteriorated since the spring of 1950. She had lost about 10 kg. She had nausea and vomiting and anorexia. *Lymphatic system:* A firm tumour can be felt in front of the left sternocleidomastoid. It is barely the size of a plum and is not tender. The surface is even and it is freely mobile relative to the skin and underlying tissues. In both groins there are a couple of enlarged lymph nodes about the size of beans and not tender. *Abdomen:* There is a hard firm tumour in the left hypochondrium stretching down to the level of the umbilicus. *Operation:* Removal from the neck of a lymph node nearly the size of a plum. *Microscopic examination U. 5812/50* (S. Ranström, M.D.): The lymph node

is thickly studded with epithelioid cell tubercles. Very little necrosis. A certain tendency to induration. This may be lymphogranulomatosis benigna. *Patho-anatomical diagnosis:* Atypical tuberculosis. The abdominal mass was later removed. *Patho-anatomical diagnosis* (U. 6468/50): Carcinoma of the suprarenal gland. *X-ray of lungs:* No abnormality.

Case 50. ♂, born 1908. Treated in hospital in 1950 under the diagnosis of lymphogranulomatosis benigna and in 1953 under the diagnosis of cystic kidney. No heredity for tuberculosis. Had come for advice about persistent pains on the right side of the neck up near the ear. An osteitic process was found in the right side of the mandible and an operation was performed. The trouble was not relieved by the operation. As there was an enlarged lymph node behind the right angle of the mandible it was removed. *Microscopic examination U. 6356/50* (S. Ranström, M.D.): The little lymph node contains numerous epithelioid cell tubercles with a considerable tendency to induration and insignificant necrosis. No giant cells. This may well be a case of lymphogranulomatosis benigna. *Patho-anatomical diagnosis:* Tuberculous lymphadenitis. — As the patient's trouble still continued a further enlarged lymph node was removed from the submental region. *Microscopic examination U. 6652/50* (Prof. Gellerstedt): Agrees well with the indurative stage of the changes in the lymph nodes in Schaumann's disease. — Having regard to the pathological reports the patient was admitted for further investigation. *Superficial lymph nodes:* On the left side of the neck below the mandible there is a fairly firm lymph node the size of a bean and, behind the sternocleidomastoid muscles, about 10 nodes ranging in size up to that of a pea. There were also some nodes in the supraclavicular fossae, in the axillae and in the groins. *X-ray of lungs:* No abnormality. *X-ray of bones of hands:* No abnormality. *Ophthalmological examination:* Conjunctivitis but no changes suggestive of l. b. *Blood:* No abnormality. *SR:* During the whole course of the disease this was low (9–12–7 mm/hr). *Fractional serum protein examination:* Total protein 6.9, albumin 3.3, globulin 3.6 %. A/G 0.92. — *Mantoux:* 0.1 mg positive. — At the end of 1952 the patient complained of abdominal pain and was readmitted for further investigation. A small cyst was found in one kidney. Guinea pig test and bacterial culture from the urine showed no tubercle bacilli. *Operation:* Resection of the cyst. This was found to be related to the renal pelvis. *Microscopic examination:* Thin-walled cyst of the ordinary type. A rounded epithelioid cell focus reminiscent of a tubercle was found in the parenchyma of the kidney.

Case 51. ♀, born 1898. The patient's husband is suffering from l. b. A younger sister had tuberculosis. Mother died of pulmonary tuberculosis in 1914. At the age of twenty the patient underwent tonsillectomy and removal of lymph nodes from the left axilla. Operated on in 1932 for bilateral tuberculous salpingitis. Repeated attacks of biliary colic since 1943. Admitted to hospital on this account in 1950. *Operation:* Cholecystectomy + removal of omental tumour. It was found incidentally at operation that there was a round, soft, greyish red tumour about the size of a hen's egg in the gastrocolic ligament. *Microscopic examination U. 9558/50* (Prof. Gellerstedt): A lymph node thickly studded with submiliary tubercles with, in general, slight induration, few giant cells and small areas of 'fibrinoid' necrosis. The histological picture resembles that seen in the lymph nodes in Schaumann's disease. *Patho-anatomical diagnosis:* Atypical tuberculosis. *X-ray of lungs:* No active lesions. *SR:* 12 mm/hr. *WBC:* 6,500, 4,800, 6,300/mm³.

Case 52. ♀, born 1912. Treated in hospital in 1950 under the diagnosis of uncompensated valvular disease of the heart + rheumatic fever? + epilepsy + post concussional syndrome? + leucopenia + lymphoma of the hilus of the left lung, and again in 1950–51 under the diagnosis lymphogranulomatosis benigna + valvular disease of the heart + epilepsy + chronic nephritis. Brother died of pulmonary

tuberculosis. Had an abortion associated with nephropathy in 1937 since when there has always been albumin in the urine. Migrains and epilepsy since 1938. The heart trouble was diagnosed in connection with the pregnancy in 1937. In 1949 the patient may have had acute polyarthritis. There was high fever and a raised sedimentation rate with pains in several joints. The enlargement of the left hilus was discovered during her stay in hospital in the beginning of 1950. It remained unchanged throughout her stay in hospital. There were no changes in the parenchyma. *Mantoux:* 0.01 mg positive. *Blood:* Leucopenia (2,100, 2,600, 2,300 WBC/mm³). *SR:* 70–102 mm/hr. *WR:* negative. In July 1950 there was swelling of a lymph node in the left supraclavicular fossa. It was suspected that the hilar lymphomata were due to some cause other than tuberculosis. She was readmitted in Nov. 1950 for further investigation. In the left supraclavicular fossa there were a couple of fairly firm, painless and freely mobile swollen lymph nodes about the size of beans. The nodes were removed. *Microscopic examination U. 9775/50* (Prof. Gellerstedt): All the lymph nodes are thickly infiltrated with submiliary, indurative tubercles in which the giant cells are scanty and there is no caseous necrosis. It looks more like Schaumann's disease than anything else. *Patho-anatomical diagnosis:* Atypical tuberculosis. *X-ray of lungs* (Jan. 1951): No change. Left hilus enlarged, showing the contours of lymph nodes bulging into the parenchyma (Fig. 3). As a result of the diagnosis of l. b., treatment with fortedol was started but had to be abandoned because of the discomfort of the patient and a great rise in the blood calcium.

Case 53. ♀, born in 1891. Treated in hospital in 1951 for a tumour in the neck. Had had tuberculosis of the left tonsil seven years earlier. Had noticed a small lump in the neck at the level of the larynx for the past year and a half. This had recently grown larger. *Local condition:* Painless, firm, mobile tumour barely the size of a pea on the anterior aspect of the neck. *Operation:* Extirpation of a well-defined tumour barely the size of a hazel nut and as hard as cartilage. *Preoperative diagnosis:* Calcified lymphoma? Tumour metastasis? *Microscopic examination U. 952/51* (S. Ranström, M.D.): The lymph node is full of numerous epithelioid cell tubercles. Occasional small necroses. Fairly slight tendency to induration. *Patho-anatomical diagnosis:* Lymphogranulomatosis benigna. *WBC:* 7,800/mm³. *SR:* 16–19 mm/hr.

Case 54. ♀, born 1893. No known contact with, or family history of, tuberculosis. Had a tumour about the size of a hen's egg on the left side by the clavicle for three years. *Operation:* Extirpation. *Microscopic examination V. 1958/51* (I. Behring, M.D.): What was removed from the neck consists of a number of enlarged lymph nodes embedded in adipose tissue. These lymph nodes are thickly studded with epithelioid-giant cell tubercles with inclusion bodies and are in a state of more or less widespread fibrosis. Nowhere caseous necrotic changes. In all probability this is a case of Schaumann's disease. *Patho-anatomical diagnosis:* Schaumann's disease.

Case 55. ♂, born 1924. Treated in hospital in 1951. Mother had pulmonary tuberculosis and died, probably of the disease. The patient had previously had enlarged lymph nodes in his neck and had had an operation on them at the age of 2–3 years. Complained of enlarged nodes under the lower jaw. They had been present for as long as the patient could remember but had grown somewhat larger in recent years. They were not tender or painful and the only inconvenience they caused was cosmetic. *On admission:* General condition good. No fever. *Superficial lymph nodes:* Two large nodes under the tip of the chin. They are at least 1 × 3–4 cm, freely mobile relative to the skin and the underlying tissues, well-defined and rounded. There is another smaller node at the angle of the jaw which is adherent to the surrounding tissue. Scar from the previous operation. *Operation:* Extirpation.

Two lymph nodes barely the size of hazel nuts were removed from the submental region. *Microscopic examination U. 4262/51* (Prof. Gellerstedt): The lymph nodes are thickly infiltrated with more or less confluent small tubercles containing sparse necroses and giant cells. These latter occasionally contain concentrically laminated foreign bodies. In some places there is slight fibrosis. The picture corresponds with that seen in the lymph nodes in Schaumann's disease. *Patho-anatomical diagnosis:* Atypical tuberculosis. — Follow-up at a central dispensary in 1951: *X-ray of lungs:* Parenchyma clear on both sides. Both hilar regions contain shadows as dense as those produced by calcification. There are also some small opacities above the upper margin of the hilus which are, in some cases, as dense as those produced by calcification. The picture is typical neither of Schaumann's disease nor of active tuberculosis. *Mantoux:* 0.05 mg positive. No skin lesions. *X-ray of bones of hands and feet:* No changes typical of Schaumann's disease. *SR:* 1/mm/hr.

Case 56. ♀, born 1902. Treated in a sanatorium in 1951. No heredity for, or known exposure to, tuberculosis. Said to have had dry pleurisy with backache and a temperature of about 39° C 12 years ago. Operated on in 1945 for gastric ulcer and a tumour (?) in the stomach. Had small nodes in the neck for many years. Apart from some fatigue there were no subjective symptoms of the illness which was discovered on routine screening of the lungs. Radiography of the lungs in June 1951 showed that the right hilar region contained bicyclically demarcated lymphomata. Also in the left hilus a shadow was seen. There were no definite changes in the parenchyma. "There may be a primary infection but the possibility of some etiological factor other than tuberculosis must also be borne in mind (neoplasm??)." *SR:* 19 mm/hr. *Mantoux:* 0.1 mg positive. Follow-up at the dispensary in Aug. 1951 showed no change in the lungs. Two lymph nodes about the size of beans were excised. *Microscopic examination U. 8136/51* (Prof. Fåhræus): Microscopically the parenchyma of the nodes is seen to be completely packed with tubercles some of which contain giant cells. The absence of caseous necrosis makes it seem probable that this is a case of *atypical tuberculosis —Schaumann's disease.*

Case 57. ♀, born 1898. Treated in hospital in 1952 for lymphadenitis of the neck. No heredity for tuberculosis. The lymph nodes of the neck and elsewhere had been growing larger for several months. She had become more tired and somewhat thinner. *On admission:* General condition normal. *Superficial lymph nodes:* There is a generalised enlargement of the lymph nodes; one of the size a prune and another somewhat smaller may be felt in the left supraclavicular fossa. Similar findings on the right side of the neck. Enlarged nodes in the groins, not particularly hard. *Abdomen:* Liver somewhat enlarged. The spleen is not palpable. *Blood:* Monocytes 10%, otherwise no abnormality. *Operation:* Extirpation of enlarged node from neck. *Microscopic examination V. 2614/52* (author): The lymph node is tightly packed with rounded tubercles with only a slight degree of caseous necrosis and few Langhans giant cells. Only a slight tendency to coalescence between the individual tubercles, but quite conspicuous perigranulomatous fibrohyalinisation. This form of tuberculous adenitis is usually characterised clinically by a prolonged course, only slight tendency to liquefaction and very little effect on the general condition (the SR is usually low). *Patho-anatomical diagnosis:* Atypical tuberculosis. *Guinea pig test:* Lymph node tissue was used and two animals were inoculated. Both died after about two months of generalised tuberculosis. *X-ray of lungs:* Some flattening of the aperture of the left thorax. In the left apical field there is thickening of the pleura and shadowy flecks in the parenchyma. The left hilus is drawn upwards with calcified deposits. There are also calcified foci in the peribronchial nodes on the right side. The X-ray investigation thus shows old tuberculous changes in the left apical field with bilateral calcification in the hilus. No definite sign of any active lesions.

Case 58. ♀, born 1898. No heredity for tuberculosis. Never had erythema nodosum or pleurisy. Troubled with increasing breathlessness over the past 5–10 years. Sometimes slight cough. Has been under observation at a central dispensary since 1945 when radiography of the lungs showed bilateral enlargement of the hili. Calcification was also seen in the left hilus and shadows in the parenchyma leading downwards from the right hilar shadow to the heart-liver angle. In the left lung there were increased markings and an irregular speckling. *Tuberculin reaction* not positive for less than 1 mg. Direct examination and cultivation of the sputum in Dec. 1945 showed no tubercle bacilli. Radiography of the lungs in 1946, 1948 and 1949 showed no change. In Nov. 1951 there was some progress in that an opacity about the size of a plum had appeared immediately lateral to the right hilus. *SR:* 1945–51 varied between 27 and 47 mm/hr. Treated in hospital in 1952 for abdominal pain. Radiography of the lungs at that time showed regression of the pulmonary lesions. Examinations of the sputum were negative. *X-ray of lungs:* Bilateral infiltration. Tomograms showed some rarefactions within the areas of infiltration. These were probably caused by their patchy distribution and partly by benign bronchiectases. A lymph node was excised from the neck for biopsy. *Microscopic examination U. 7311/52* (S. Ranström, M.D.): There are many epithelioid cell tubercles in the lymph node. Some small areas of caseous necrosis and a considerable tendency to induration. It looks more like an ordinary case of tuberculosis but the possibility of Schaumann's disease cannot be ruled out. — Admitted to a sanatorium for chemotherapy. *On admission:* General condition good. *Pirquet's reaction:* Negative. *Mantoux:* 0.1 mg positive. *WBC:* 5000/mm³. *Histoplasmin and coccidioidin tests:* Negative. *Fractional serum protein examination:* Total protein 6.6, albumin 2.7, and globulin 3.9 %. A/G 0.7. Repeated examination and cultivation of the sputum gave negative results. Guinea pig tests with gastric lavage fluid was negative.

Series II

Lymph Nodes Without Bacilli. Lymphogranulomatosis Benigua

Case 1. ♀, born 1865. Treated in hospital Nov. 1935 to Jan. 1936 under the diagnosis of tuberculous lymphoma + femoral hernia + healed pulmonary tuberculosis + hypertension. At operation for the hernia a fairly firm lymph node about the size of a marble was removed from just above the fossa ovalis in the left groin and three smaller ones about the size of hazel nuts were found in the neighbourhood and removed. *Microscopic examination U. 2187/35* (Prof. Gellerstedt): The lymph node is very thickly packed with small miliary and submiliary tubercles, many containing atypical giant cells. The complete absence of caseous necrosis and the marked tendency to sclerosis, more in the reticulum of the intervening connective tissue than in the tubercles themselves are striking. The picture of an atypical tuberculosis of this sort makes one think that this may be a case of the Mylius & Schürmann variety of tuberculosis. *Patho-anatomical diagnosis:* Tuberculosis. — As a result of the patho-anatomical diagnosis an X-ray investigation of the lungs was made which showed large heavy hilar shadows. On the right side the bronchial shadows were very pronounced and there was diffuse opacity, partly in the form of small flecks.

Case 2. ♀, born 1901. Treated in hospital in 1936 under the diagnosis of neurasthenia + secondary anemia, also later in the same year under the diagnosis of tuberculous lymphoma + splenomegaly + acute sinusitis. In 1948 treated for chronic bronchitis and pneumonia and again in 1950 under the diagnosis of pul-

monary fibrosis and fibrinous pericarditis. — No known exposure to or heredity for tuberculosis. Had respiratory catarrh in winter 1935 with severe cough. After this felt tired and ill and had slight fever. *On admission* (1936): General condition good. Thin. *Superficial lymph nodes:* In both sides of the neck as well as in the axillae and groins there were firm elastic lymph nodes ranging in size between that of a haricot and that of a grain of corn. They were not tender. *Heart:* Soft blowing systolic murmur. *Abdomen:* The lower pole of the spleen is clearly palpable in the left flank and on deep breathing it reaches two finger's breadths below the costal margin. Consistency fairly hard. *Blood:* Eosinophils 2.5–5.5 per cent, monocytes 8–18 %. *SR:* 78 mm/hr. on admission, 10 mm/hr. on discharge. *Mantoux:* 1 mg negative. *WR:* Negative. *Blood culture:* Negative after repeated attempts. Extirpation of a lymph node. *Microscopic examination U. 1284/36* (Prof. Fåhræus): The lymph node consists almost exclusively of typical giant cell tubercles which show a strong tendency to fibrosis but little caseation. *Patho-anatomical diagnosis:* Tuberculosis. — *X-ray of lungs:* Enlargement of the hilar shadows with considerable increase in the markings round the hili. — Treated for pneumonia at home in 1946. Since 1948 has suffered from cough, sever shortage of breath and heart trouble. These troubles became worse in 1950, so she was admitted to a hospital. She showed considerable breathlessness and cyanosis and died presenting a picture of heart failure. *Autopsy:* Fibrosis of the lungs and fibrino-hemorrhagic pericarditis. The microscopical examination (Prof. O. Reuterwall) confirmed the previous diagnoses. Here and there in the lungs there were collections of epithelioid cells with an occasional Langhans giant cell.

Case 3. ♂, born 1911. Treated in hospital in 1936 under the diagnosis of tuberculous lymphoma of the hili of the lungs + tuberculous lymphoma of the neck and also treated in the same year in a sanatorium under the diagnosis of lymphogranulomatosis benigna. A paternal aunt with whom the patient had been in contact had had tuberculosis but there was no other known source of infection. In Dec. 1935 tired and weak, slight fever. *On admission* (in Feb. 1936):– *Superficial lymph nodes:* No abnormality. *RBC:* 4.1 mil/mm³. *WBC:* 4,100 /mm³. Eosinophils 7 %, monocytes 11 %. *SR:* About 20 mm/hr. *X-ray of lungs* (Feb. 1936): Hilar shadows considerably enlarged and dense. Considerably increased mossy markings round both hili, especially above the right one. *X-ray* (May 1936): No noteworthy change. — In May 1936 some nodes were found below the mandible ranging in size up to that of a hazel nut. Below the angle of the mandible on the right side and in front of the sternocleidomastoid there was a lymph node almost as big as an almond. Extirpation of a lymph node. *Microscopic examination* U. 1393/36 (Prof. Fåhræus): The lymph node is studded with typical tubercles which show both peripheral fibrosis and central caseation. *Patho-anatomical diagnosis:* Tuberculosis. — On admission to the sanatorium the patient was found to be tuberculin negative (Mantoux 1 mg). Repeated examinations of the sputum were negative. In August there was found to be a bundle of nodes on each side of the neck. They were hard but not tender. There were also a couple of enlarged nodes in the left groin about the size of almonds. All these nodes showed a certain amount of periadenitis. *SR:* 19 mm/hr. Eosinophils about 12 %; monocytes 7–10 %. — In the beginning of Oct. 1936 the patient became noticeably apathetic with slight stiffness of the neck. *Investigation of the C.S.F.:* No increase in the number of cells. Pandy +, Nonne −. A couple of weeks later the results were: Cells 4/mm³, Pandy +, Nonne −. The patient grew steadily worse and died in the beginning of Nov. 1936. *Autopsy* (G. Birath, M.D.): The left lung was hyperemic and oedematous but showed no other lesions. The upper lobe of the right lung was firmer than normal. Section of the parenchyma showed that it was thickly studded with extremely small specks. Similar lesions were to be seen in the lower lobe. The hilar nodes were considerably enlarged on both sides and their cut surface was greasy and greyish red and partly pigmented with carbon particles. The paratracheal nodes were also noticeably

enlarged. The spleen was greatly enlarged. It was about 20 cm long and of firm consistency and the cut surface was blackish red. Brain: No abnormality. *Microscopic examination* (Prof. H. Bergstrand): Sections from the lung and lymph nodes as well as from the liver and spleen show numerous epithelioid cell tubercles with giant cells of the Langhans type. The picture differs, however in one noteworthy way from that seen in tuberculosis in that, in spite of the extensiveness of the process, there are hardly any necroses to be seen in the tubercles. This is suggestive of lymphogranulomatosis benigna. The lungs in particular were therefore searched especially carefully with a view to demonstrating the concentric bodies which are characteristic of the condition. Such bodies were demonstrated in quite large numbers, and there should consequently be no doubt as to the diagnosis.

Case 4. ♀, born 1882. Treated in hospital in 1936 under the diagnosis of lymphogranuloma benignum. No known contact with or heredity for tuberculosis. The patient went to a physician on account of heart trouble and a couple of swellings above the collar bone. *X-ray of the lungs* showed enlargement of the hilar lymph nodes. She was admitted to hospital as a suspected case of some disease of the blood. *On admission:* General condition normal. Slight fever. *SR:* 24 mm/hr. *Superficial lymph nodes:* There are two palpable lymph nodes in the left supraclavicular fossa, one the size of a walnut and the other the size of a hazel nut. They are mobile and not tender and are not fixed to one another. In the right supraclavicular fossa there is another mobile node about the size of a hazel nut. There are also a couple of small nodes in the axillae. *Abdomen:* No abnormality. *Skin:* There is a patch of redness above the left ankle about the size of a hen's egg. It is infiltrated but not very tender (declining erythema nodosum?). *RBC:* 5.0 mil/mm³. *WBC:* 5.400/mm³. Eosinophils 2.5–5.5 %, monocytes 5–9.5 %. *Mantoux:* "Weakly positive." Extirpation of a lymph node. *Microscopic examination U. 2963/36* (Prof. Gellerstedt): The picture corresponds quite well with lymphogranuloma benignum. It consists of an epithelioid cell tuberculosis, the tubercles being miliary or submiliary, showing no caseous necrosis. Only rudimentary forms of giant cells. A fairly marked tendency to sclerosis of the lymphoid reticulum. It would appear desirable to look for cystic destruction of the bones of the fingers and toes as well as non-ulcerative lesions of the skin, enlargement of the spleen etc. The weakly positive Mantoux reaction suggests that the above diagnosis is correct. *Patho-anatomical diagnosis:* Atypical tuberculosis. — *X-ray of bones of hands:* No changes suggestive of Schaumann's diesase.

Case 5. ♀, born 1877. Treated in hospital and sanatorium in 1937 under the diagnosis lymphogranulomatosis benigna. A nephew of the patient's husband had died of tuberculosis about 20 years before and a grandson was suffering from tuberculosis at the time of admission. The patient had been in contact with both cases. No erythema nodosum or pleurisy. Had been coughing a lot for the past two years, especially during the winter. While the patient was undergoing treatment for a femoral hernia in 1937 a radiograph of the lungs was taken which showed patchy shadows over the greater parts of both lung fields, especially dense over the lower $^{2}/_{3}$ of the right lung field. Six sputum tests were negative. The patient was admitted to sanatorium. *On admission:* General condition fairly good. *Superficial lymph nodes:* In the right axilla there was a fairly soft node about the size of an almond and in the other axilla and both groins there were nodes ranging in size up to that of a pea and of firm consistency. *SR:* 52 mm/hr. *WBC:* 5,600/mm³. *Differential counting* revealed monocytosis (13–17 % monocytes). *WR:* Negative. *Mantoux:* 3 mg negative. *X-ray of lungs* (5.8. 1937): Since the previous X-ray examination (4.6. 1937) the infiltration has increased somewhat below the right hilus and lateral to and slightly below the left hilus. Small amount of fluid at the right base. ? nature of process. Carcinomatous lymphangitis? Tuberculosis?? — *X-ray of bones of hands:* In the distal part of the middle phalanx of the 4th finger

of the left hand and the 3rd finger of the right hand there are some small areas of rarefaction. Extirpation of a lymph node from the right axilla. *Microscopic examination U. 2499/37* (Prof. Gellerstedt): Lesions in the lymph node are such as are seen in Schaumann's or Mylius & Schürmann's disease: Epithelioid cell tuberculosis with some giant cells, without necrosis but with beautiful hyaline sclerosis of the basal reticulum. — Are there any radiographically demonstrable changes in the bones of the hands or feet, skin lesions etc.? Pulmonary lesions? *Patho-anatomical diagnosis:* Atypical tuberculosis. — After repeatedly negative results had been obtained in searching for acid-fast rods in the sputum and after two unsuccessful attempts at cultivating tubercle bacilli they were successfully grown in a Hohn-Loewenstein tube in Nov. 1937. Microscopic examination of these colonies showed the presence of thick rod-shaped or coccoid acid-fast bacteria which gave rise to progressive tuberculosis in guinea pigs and which proved, on typing in rabbits, to be of the human type. In Dec. 1937 two guinea pigs were inoculated with sputum from the patient, one intraperitoneally and the other subcutaneously. Post mortem examination of the first showed foci of caseous degeneration in the spleen and mesentery. Microscopic examination revealed the presence of acid-fast rods. There were no definite lesions in the guinea pig which had been inoculated subcutaneously. — When followed up in May 1939 the patient complained of breathlessness. She was then kyphotic. *X-ray of spinal column:* Destruction and collapse of L_2–L_3 with destruction of the disc. Radiographic diagnosis of tuberculous spondylitis. Died Nov. 1939. Cause of death unknown, probably tuberculosis.

Case 6. ♀, born 1886. Treated in hospital in 1934 for an unexplained rise in SR and fever and several times during the years 1938–1940 under the diagnosis uveoparotid fever. Had a cough and sore throat about Christmas 1933. This was associated with bilateral enlargement of the parotid glands. During her stay in hospital in 1934 it was noticed that there was a hard lymph node the size of a bean in the right axilla and right groin as well as enlargement of the parotid glands. *WBC:* 6,000/mm³. Eosinophils 0%, monocytes 11%. *SR:* 124 mm/hr. *X-ray of lungs:* Hili somewhat enlarged. Increased vascular markings in the parenchyma. A rather shadowy area below the right hilus. On admission the temperature was 40° C and stayed there for a short while. *Ophtalmological investigation:* No abnormality. — Since discharge in 1934 a painful swelling had arisen suddenly beneath the ears every five years or so and had been accompanied by high fever. Ever since the first of these attacks the patient had felt dry in the mouth. Treated in a cottage hospital on a couple of occasions for acute septic parotitis. On one of these occasions an incision was made and a pus-like liquid escaped. Moderate enlargement of the parotid glands and a generalised slight enlargement of the lymph nodes were observed during the patient's periods of hospital treatment in 1938–40. There were also petechial hemorrhages, especially on the legs. Low thrombocyte value. *Mantoux:* 2 mg negative. *WBC:* 3,000–4,400/mm³. In 1937 BCG vaccination was carried out on the left upper arm. As this had no effect a new inoculation was made in Jan. 1938, this time on the right upper arm. A small area of infiltration gradually developed at the site of inoculation and at the same time an area of redness and swelling appeared at the site of the previous inoculation on the other arm. Tuberculin testing carried out in June 1938 gave a positive result with 1 mg. Extirpation of lymph node. *Microscopic examination U. 223/38* (Prof. Fåhræus): The lymph node contains a large number of rounded foci of epithelioid cells without either giant cells or caseous necrosis. Nor is there any tendency towards fibrosis. *Patho-anatomical diagnosis:* Lymphogranulomatosis benigna. — *X-ray of lungs* (1949): Emphysema, scattered areas of bronchiectasis and peribronchial infiltration over both bases. Small calcified focus in the left hilus. Slight thickening of the pleura over both apices. No visible swelling of the lymph nodes within the thorax. *Fractional serum protein analysis* (March 1944):

Total protein 9.5, albumin 4.2 and globulin 5.3 %. A/G 0.9. — When the patient was in hospital in 1937 examination of the eyes showed a large amount of greyish white precipitate on the right membrane of Descemet. The iris showed blurring of the normal markings and a punctate greyish infiltration. There was also scattering of the light in the anterior chamber but no precipitate. There were no definite lesions in the fundi. *Diagnosis:* Uveitis of the right eye. The picture of kerato-conjunctivitis gradually developed in both eyes.

Case 7. ♀, born 1912. Treated in hospital in 1938–39 under the diagnosis of Schaumann's disease. No heredity for or known exposure to tuberculosis. Admitted on account of abdominal pain. *Superficial lymph nodes:* No abnormality. *Abdomen:* No abnormality. — The abdominal pain soon disappeared but the patient had a slight fever during the whole of her stay in hospital and her SR rose from 66 to 105 mm/hr. *RBC:* 4.2 mil/mm³. *WBC:* 5,000–7,700/mm³. *WR:* negative. *Mantoux:* 4 mg negative. *Differential blood count:* Eosinophils 2 %, large monocytes and transitional forms 12 %. — A couple of months later there were two or three painless mobile lymph nodes barely the size of peas in the right side of the neck. There was a similar node at the angle of the jaw. Exstirpation of lymph node. *Microscopic examination U. 134/39* (Prof. Gellerstedt): The whole lymph node is packed with submiliary epithelioid cell foci of equal size, some of which contain a little central necrosis. Some giant cells not unlike those of Langhans. The hyaline sclerosis of the lymphoid reticulum between the tubercles is more or less pronounced. Apart from the caseous necrosis and giant cells the picture is that seen in the lymph nodes in classical cases of Schaumann's disease. *Patho-anatomical diagnosis:* Atypical tuberculosis. *X-ray of lungs:* There are large lesions within both lung fields taking the form of streaks and flecks radiating from the hili. The right border of the mediastinum is more convex than usual. "Although the picture is not altogether typical, there is not much choice of diagnosis apart from tuberculosis (cf. the conditions belonging to the group of lymphogranulomatoses, Schaumann's disease, etc.)." Repeated re-examination of the lungs showed the same general picture, the last was in Sept. 1939. At that time the *SR* was 91 mm/hr. *Died* 1943. *Cause of death:* Pulmonary tuberculosis. No autopsy.

Case 8. ♀, born 1912. Treated in hospital several times under the following diagnoses: Porphyrinuria (1936), Lymphogranulomatosis benigna? (1937), Acute pharyngitis + acute lymphadenitis of the neck [lymphogranulomatosis benigna?] (1940), Exudative pericarditis (1944), Acute meningitis (1945). One sister died of pulmonary tuberculosis in 1922. — Often had catarrh of the throat. About 1932 had influenza with aching in the back and fever. Dark urine. *Diagnosis:* Porphyrinuria. *SR:* 11 mm/hr. 1937 cough. *X-ray of lungs:* Small spots in both apical regions. *Sputum:* No tubercle bacilli. *Mantoux:* 3 mg negative. *Blood:* No abnormality. *WR:* Negative. — 1939, tired and short of breadth. Pains in the chest. A lymph node the size of a pea was felt in the right groin. *Mantoux:* Still negative. Biopsy of lymph node. *Microscopic examination U. 3098/39* (Prof. Gellerstedt): The lymph node is partly infiltrated with submiliary tubercles lying in groups and formed of epithelioid cells. Giant cells are only occasionally to be seen. Also, necroses are only seen in the larger masses of tubercles. This is thus a picture of Schaumann's disease though not altogether typical, particularly because the tendency to fibrous induration is not present. *Patho-anatomical diagnosis:* Atypical tuberculosis. — In 1940 the lymph node of both sides of the neck swelled and there was a rise in temperature. The swollen nodes were tender. *SR:* 37 mm/hr. *Mantoux:* Still negative. In 1944 the patient became suddenly ill with fever and chills. *X-ray examination* showed marked enlargement of the heart and exudative pericarditis. *Mantoux:* 0.1 mg now positive. In 1945 the patient suddenly became ill with symptoms of meningitis. Meningococci were demonstrated in the cerebrospinal fluid. *X-ray of lungs:* Large new pleural thickening on the left side.

Case 9. ♂, born 1902. Treated in hospital several times during the years 1940–43. Diagnoses: Lymphogranulomatosis benigna (1940). Lymphogranulomatosis benigna + duodenal ulcer (1941), Lymphogranulomatosis benigna + chronic nephritis + duodenal ulcer (?) (1943). No heredity for tuberculosis. Tonsils removed in 1923 on account of repeated attacks of severe sore throat. In May 1939 the patient noticed a swelling of the lymph nodes of the right groin. It disappeared but returned in the spring of 1940. *Superficial lymph nodes:* There was a general enlargement of the superficial lymph nodes, under the angle of the jaw they were the size of almonds, in front of the sternocleidomastoid that of peas while in the groins and axillae they reached nearly the size of pigeon's eggs. They were all soft, smooth, mobile and not tender. *Abdomen:* Spleen palpable. *WBC:* 3,000–5,200/mm³. Eosinophils 2 %, monocytes 7 %. *SR:* 9–18 mm/hr. *X-ray of spleen:* Significant enlargement. Extirpation of an axillary lymph node. *Microscopic examination U. 1136/40* (Prof. Fåhræus): The enlarged lymph node is crammed with epithelioid cells arranged in rounded groups like tubercles. There are, however, no caseous necroses whatever, nor are there any giant cells, so that the picture corresponds exactly with that of lymphogranuloma benignum. *Pathoanatomical diagnosis:* Atypical tuberculosis. — *Mantoux:* 1 mg negative. *X-ray of bones of feet:* No abnormality. *X-ray of lungs:* Large shadows of nodes in both hili, close to and below the right hilus and in the paratracheal regions on both sides. No lesions in the parenchyma itself apart from moderate emphysema and some basal bronchiectases. *Ophthalmological investigation:* Kerato-conjunctivitis sicca. — *SR:* 41–51 mm/hr. *Sputum:* Repeated investigations negative. — The cause of the patient's admission in 1943 was his continual stomach trouble. *X-ray investigation* showed marked deformity of the duodenal cap. *WBC:* 5,500/mm³. Eosinophils 7 %, monocytes 5 %. *X-ray of lungs:* No change. — The signs which aroused a suspicion of nephritis were positive Heller and a few white cells in the urine. There was a moderate increase in the non-protein nitrogen of the blood.

Case 10. ♂, born 1893. Treated in the Finsen Institute in Stockholm for lupus erythematodes of the face. Some painless lymph nodes discovered in both groins in 1941. These gradually grew larger. Increasing tiredness in 1942. Admitted to hospital for investigation. *On admission* (1942): General condition good. *Skin:* On the forehead and bridge of the nose remains of treated lupus erythematodes. *Superficial lymph nodes:* On both sides of the neck and in the axillae and groins there were a number of firmly elastic, freely mobile, painless lymph nodes ranging up to the size of a bean. *Abdomen:* Liver palpable a bare finger's breadth below the costal margin. Spleen not palpable. *Blood:* No abnormality apart from 6 % eosinophilia. *Screening of lungs:* Hili very slightly broadened with diffuse blurring of the boundaries. Exstirpation of a lymph node. *Microscopic examination U. 509/42* (Prof. Gellerstedt): The lymph node is closely and diffusely studded with submiliary epithelioid cell tubercles without caseous necrosis but with many giant cells some of which are atypical. There is, however, definite, though not very pronounced, sclerosis of the basal reticulum between the tubercles. The picture is somewhat reminiscent of the changes seen in the lymph nodes in Schaumann's disease. The characteristic foreign bodies which are sometimes to be seen in the giant cells in this condition are, however, absent in the present case. *Pathoanatomical diagnosis:* Atypical tuberculosis. — *Mantoux:* 0.01 mg positive.

Case 11. ♀, born 1885. Treated in hospital in 1942 under the diagnosis of lymphogranulomatosis benigna. No heredity for tuberculosis. About 1940 the parotids began to swell. This was associated with dryness of the mouth. In 1941 the submandibular glands also began to swell. Had a slight fever during two years. *On admission* (in 1942): General condition good. *Superficial lymph nodes:* On both sides of the neck and in the groins and cubital regions there are mobile lymph nodes, some as large as pigeon's eggs. They are freely mobile and not tender. The

parotid glands are as hard as cartilage and the size of the palm of a hand. *SR:* 46 mm/hr. *Blood:* Monocytes 17 %, otherwise no abnormality. Extirpation of a lymph node from the neck. *Microscopic examination U. 1354/42* (Prof. Gellerstedt): The picture corresponds fairly well with the changes seen in the lymph nodes in Schaumann's disease though it is possible to see traces of caseous necrosis which, as a rule, is not found in that condition. No acid-fast rods could be demonstrated. — *Mantoux:* 1 mg negative. *X-ray of lungs:* Adhesions in both sinus. Both hili are enlarged and more dense than usual, especially the right. There is an increase in the markings radiating from the right hilus to the base. There is a suspicious speckling of the parenchyma. *X-ray of bones of hands:* No abnormality.

Case 12. ♂, born 1927. Treated in hospital in 1943 under the diagnosis of Schaumann's disease. No heredity for or known contact with tuberculosis. Had lost 10 kg during the previous 4 months and had noticed swelling of the lymph nodes of the neck. *Superficial lymph nodes:* On both sides of the neck and in the axillae and groins there are palpable lymph nodes ranging up to the size of a bean. *SR:* 20 mm/hr. *Blood:* Moderate anemia. 12 % eosinophils. Extirpation of a lymph node. *Microscopic examination U. 2058/43* (Prof. Fåhræus): The lymph node is closely packed with tubercles. They are, in general, all in the same stage of development and show only a slight tendency to caseous necrosis. Only occasional giant cells. Schaumann's disease? *Patho-anatomical diagnosis:* Atypical tuberculosis. — *Mantoux:* 1 mg negative. In 1944 there appeared lesions of the cheeks looking like lupus pernio. *Ophthalmological investigation:* Chronic uveitis. *X-ray of lungs:* Large shadows of lymph nodes in the right hilus and an oblong and rather more dense opacity in the right mediastinum. The left hilus shows no changes. — No skeletal abnormality. Inoculation of a guinea pig and culture on Loewenstein's medium of material from the lymph node gave negative results. *Fractional serum protein analysis:* Total protein 6.8 % of which 3.3 % globulin. A/G 1.1.

Case 13. ♂, born 1907. Examined as an out-patient at a central dispensary. 4 year old daughter had tuberculosis. — Bilateral enlargement of the hili found in March 1940. *X-ray of lungs* (1941): Shadows of enlarged hilar nodes on both sides (Fig. 25). No changes in the parenchyma. Picture unchanged since 1940. — Erythema induratum like skin lesions on both lower legs in Sept. 1941. A lymph node the size of a chestnut was felt in the right axilla in April 1942. It was removed. *Microscopic examination V. 2455/43* (I. Behring, M.D.): The lymph node is very densely infiltrated with foci of epithelioid cells which are confluent in places. Some giant cells mostly of the Langhans type. Inclusion bodies are to be seen in them in several places. There is no trace of caseous necrosis. Furthermore there is no marked perifocal reaction. There is, however, in some places, a certain amount of fibrosis and hyalinisation of the foci. *Patho-anatomical diagnosis:* Schaumann's disease. — *X-ray of lungs* (1944): No change. *X-ray of lungs* (1947): Definite decrease in size of the hilar lymph nodes. No sign of active tuberculosis. *SR*: Low throughout the course of the illness (May 1941 4 mm/hr.). *Blood:* No abnormality.

Case 14. ♀, born 1888. Treated in hospital in 1937 under the diagnosis of bilateral chronic iridocyclitis, also in 1943 under the diagnosis of acute hepatitis. No heredity for tuberculosis. Became ill in Sept. 1943 with severe abdominal pain and progressive icterus. Laparotomy. The gall bladder was thin walled and under strong tension. It was punctured but no stones were palpable in it. The liver was found to be greatly enlarged with a swollen rounded border. There were many enlarged lymph nodes in the porta hepatis. One the size of an almond and of a greyish white colour was removed. *Microscopic examination U. 3995/43* (Prof. Gellerstedt): The whole of the lymph node is thickly infiltrated with submiliary groups of epithelioid cells. These contain large numbers of giant cells of varying size but no caseous necroses. The basal reticulum is not sclerosed or thickened

between the foci. The giant cells often contain peculiar inclusions of a kind which I have frequently found in the giant cells of Schaumann's disease. The general appearance of the histological picture also is what one would expect to see in a case of this condition. — The patient's lungs were examined radiologically as a result of this patho-anatomical diagnosis. The picture showed bilateral enlargement of the hili and small diffusely scattered opacities in the parenchyma of both sides. *SR:* 38 mm/hr. *Mantoux:* 0.1 mg positive.

Case 15. ♂, born 1902. Treated in hospital in 1947 under the diagnosis of lupus erythematosus disseminatus? Schaumann's disease??, and again in 1947 under the diagnosis of Schaumann's disease + chronic nephritis? No heredity for tuberculosis. Had rheumatic fever in 1939 after which he felt quite well until 1942 when a couple of toes began to swell. In 1944 the swelling of the lymph nodes of the neck began. Extirpation of a lymph node. *Microscopic examination U. 2742/44* (Prof. J. Mellgren): The lymph node is the size of a hazel nut and is tightly packed with groups of epithelioid cells in some of which there is central caseation. No giant cells. No tubercle bacilli seen. This is thus the picture of Schaumann's disease. *Patho-anatomical diagnosis:* Atypical tuberculosis. — In 1945 the skin of the nose began to swell and get red. *X-ray of lungs* (1947): Bilateral affection of the hili with basal atelectases. *X-ray of feet:* Marked destruction of the bones. *Mantoux:* 3 mg negative. *Heller:* Constantly positive. The urinary sediment contained few cells. *Final note* (1947): "The protracted course of the illness, the joint troubles with fever, the pleural thickening and changes in the skin, the enlargement of the lymph nodes and the nephropathy all suggest that this is a case of lupus erythematosis disseminatus, a condition which has a less favourable prognosis than Schaumann's disease." — When the patient came under treatment in 1948 the condition was more or less the same. Non-protein nitrogen in the serum somewhat raised, moderate but constant albuminuria. The urinary sediment contained some red corpuscles. The patient also manifested neurological symptoms in the form of dizziness. *SR:* 40–55 mm/hr.

Case 16. ♂, born 1907. Treated in sanatorium in 1944. Brother died of tuberculosis. In Jan. 1942 a "spot" was demonstrated radiographically on one lung. In May 1944 he had an obstinate cough with fever. Radiography revealed definite enlargement of the hilar shadows also diffuse opacities in the first and second right intercostal spaces and the left basal region. No tubercle bacilli in the sputum. Culture and guinea pig tests with gastric lavage fluid gave negative results for tuberculosis. There were a number of firm enlarged lymph nodes in the neck and in the axillae. *SR:* 13 mm/hr. *Mantoux:* 0.01 mg positive. As the X-ray picture suggested Schaumann's disease, one of the enlarged supraclavicular nodes was removed for biopsy. *Microscopic examination U. 4931/44* (Prof. Gellerstedt): The whole node is infiltrated with uniform submiliary tubercles with a decided tendency to sclerosis of the basal reticulum. Occasional giant cells and a few minimal caseous foci. This corresponds with the picture seen in the lymph nodes in Schaumann's disease. *Patho-anatomical diagnosis:* Atypical tuberculosis. — Follow-up X-ray in June 1945 showed considerable diminution of the shadows of the lymph nodes at the hili. Some enlarged lymph nodes the size of almonds were found in the neck.

Case 17. ♂, born 1913. No heredity for or known contact with tuberculosis. Treated in hospital in 1942 under the diagnosis of pneumonia + acute myocarditis. *X-ray of lungs:* A soft tissue shadow the size of a walnut in the left hilus, also small lesions of the parenchyma with diffuse margins partly outside the left border of the heart and partly laterally on a level with the right hilus. — The diagnosis of l. b. was first made in 1945 when screening of the lungs gave a positive result. The tuberculin reaction was negative in 1944 and 1945. At that time the patient

had been troubled with "asthma" for two years. He was admitted to sanatorium in June 1945 and treated there under the diagnosis of Schaumann's disease. — *Superficial lymph nodes:* The size of beans bilaterally on both sides of the neck and in the left axilla, the size of hazel nuts in the right axilla, barely the size of beans in each groin. *X-ray of lungs:* Both hili somewhat denser than normal. There is a marked and fairly uniform streakiness of both lungs and also, scattered uniformly through the parenchyma of both sides, a miliary speckling. The lesions are well defined. On the right side there is an interlobar streak. *X-ray of bones of hands and feet:* A cystic area of rarefaction barely the size of a pea. *SR:* 15–36 mm/hr. *Mantoux:* 1 mg negative. Extirpation of a lymph node. *Microscopic examination S. 1408/45* (F. Wahlgren, M.D.): The lymph node is tightly packed with small rounded foci of epithelioid cells which look like tubercles and touch one another. In some of these there are giant cells of Langhans' type. Here and there traces of caseous necroses, as well as the beginnings of fibrous induration. The histological picture is reasonably typical of *lymphogranuloma benignum.* No tubercle bacilli were demonstrated.

Case 18. ♀, born 1887. Treated in hospital in 1944 under the diagnosis of Schaumann's disease. No heredity for tuberculosis. Never had erythema nodosum or pleurisy. Tired during the past two years, become short of breath and noticed palpitations. Coughed. *X-ray of lungs* (1944). Pronounced fibrotic changes, especially on the right side immediately above and below the clavicle. Admitted to sanatorium in 1944. *Tuberculin test:* negative. *Guinea pig test* using gastric lavage fluid negative. An eruption appeared on the arms and legs during the summer of 1944. *Condition* (in 1945): – *Skin:* There are closely set, dry, light reddish brown patches not larger than beans or peas on the skin of the arms, legs and back. *Superficial lymph nodes:* There are a few small painless nodes in the neck and also some, not larger than beans in both groins. *Eyes:* Conjunctivitis. *Blood:* Monocytes 9%, otherwise nothing noteworthy. *SR:* 33–48 mm/hr. Removal of two lymph nodes from the right groin and a piece of eruption from the right thigh. *Microscopic examination U. 2478/45* (Prof. Gellerstedt): In the skin, and even more in the lymph nodes, there is the picture of atypical tuberculosis characteristic of Schaumann's disease. *Patho-anatomical diagnosis:* Schaumann's disease. — Died at home in 1945. No death certificate. Cause of death given as cancer + heart failure.

Case 19. ♂, born 1917. Treated in hospital in 1946 under the diagnosis of tuberculous lymphadenitis of the region of the papilla of Vater with icterus. One brother has tuberculosis and is receiving sanatorium treatment. — The patient had sudden attacks of abdominal pain which passed off equally suddenly during the past two years. In Jan. 1946 he fell ill with symptoms suggestive of influensa: Temp. 39° C, pains in the back and legs. After a couple of days the temperature returned to normal. About a week later nausea and vomiting. Yellowish staining of the skin, pale faeces and yellow urine. Admitted to hospital. *Meulengracht:* 24. *SR:* 46 mm/hr. *Exploratory laparotomy:* Very large, soft lymph nodes, some as large as walnuts lying behind the common bile duct in the region of the papilla of Vater. One of these was taken for biopsy. *Microscopic examination U. 851/46* (Prof. Gellerstedt): A lymph node which contains small groups of fairly typical tubercles without caseous necrosis or giant cells but with a certain tendency towards fibrosis. Are there any indications of Schaumann's disease? — *Mantoux:* 1 mg negative. *X-ray of lungs:* No abnormality in May and Nov. 1946. *WBC:* 7,300/mm³. Eosinophils 5%, monocytes 6%.

Case 20. ♀, born 1924. Treated in hospital in 1946 under the diagnosis of acute polyarthritis + Schaumann's disease. No heredity for tuberculosis. Fell ill 3 weeks before admission to hospital with pains, swelling and redness in the knees and ankles. After a couple of weeks the trouble appeared in the right wrist and thumb

joints. *On admission:* General condition satisfactory. *Tonsils:* Normal. *Superficial lymph nodes:* No abnormality. *Joints:* Swelling around both ankle joints with pain on movement. Considerable swelling of the capsule of the knee joints. The basal joint of the right thumb is the seat of moderate periarthritis with swelling and redness of the skin. In the left wrist there is some swelling with limitation of movements owing to pain. *SR:* 38 mm/hr. *Blood:* Slight anemia, otherwise no abnormality. *Mantoux:* 1 mg negative. *X-ray of lungs* (7.6. 1946): Enlargement of hilar glands? — A couple of firm painless lymph node about the size of haricot beans were felt in the right supraclavicular fossa. *Spleen:* Not palpable. — Extirpation of a lymph node. *Microscopic examination U. 3957/46* (Prof. Gellerstedt): Submiliary tubercles tightly clustered together throughout the lymph node. Occasional giant cells. No caseation. Corresponds with the picture seen in the lymph nodes in Schaumann's disease. *Patho-anatomical diagnosis:* Atypical tuberculosis. *Repeat X-ray of lungs* (26.6. 46): Both hili are enlarged and dense, especially the right. Interlobar pleurisy. — Later radiographs check up showed a net-like mottling of the parenchyma. In Sept. 1946 there was regression of the changes both in the hilus and in the parenchyma. In Jan. 1948 there was further regression and a lowering of the SR. Follow up in 1951 showed the patient to be subjectively healthy.

Case 21. ♂, born 1912. No heredity for or known contact with tuberculosis. Previously in good health. Visited a physician on account of an injury to the knee in Dec. 1947 when enlarged nodes were found in the groins. *Mantoux:* Negative. Extirpation of lymph nodes. *Microscopic examination Umeå 2563/47* (Dr. C. W. Lundqvist): The lymph nodes are studded with large numbers of large and small epithelioid cell tubercles with giant cells which are often of the foreign body type. Here and there one of these giant cells contains a calcified foreign body of undetermined nature. No tubercle bacilli demonstrated. The microscopic picture is more suggestive of lymphogranuloma benignum than anything else. *Patho-anatomical diagnosis:* Lymphogranulomatosis benigna. *WBC:* 6,100/mm³. Eosinophils 2.5 %, monocytes 9.5 %. *X-ray of lungs* (Dec. 1947): Negative. — The patient remained free from symptoms until Nov. 1948 when he became suddenly ill with a temperature of up to 40° C. and signs of upper respiratory tract infection. Admitted to hospital Dec. 1948. At this time the Mantoux test was positive. *SR:* 54 mm/hr. *On admission:* General condition satisfactory in spite of high fever. *Superficial lymph nodes:* Some soft painless nodes about the size of haricot beans under each angle of the jaw. Also several painless and relatively soft nodes of somewhat greater size in the axillae. In both groins there were enlarged nodes, some as large as plums and others smaller. *Abdomen:* Palpable spleen. *X-ray of lungs:* Increased density of the parenchyma in both bases radiating from the hili which are enlarged. (Fig. 26.) — Removal of inguinal nodes. *Microscopic examination U. 19/44* (author): The lymph nodes are largely filled with miliary tubercles which are often confluent and usually the seat of marked connective tissue induration. In some of the more recent tubercles there are minimal caseous necroses. In the older granulomata there are some giant cells of the Langhans type many of which contain concentrically lamellated bodies which stain blue with hematoxylin. Three acid-fast rods demonstrated in tubercles showing caseation. *Patho-anatomical diagnosis.* Tuberculosis (miliary?). — Streptomycin treatment was instituted as a result of the finding of the bacilli. Guinea pig test using finely divided lymph nodes positive. In Jan. 1949 X-ray of the lungs showed slight improvement. In March the patient's general condition was definitely better. The spleen, which had earlier been easily palpable was now scarcely to be felt. The lymph nodes, however, were much the same as before. In April 1949 radiography of the lungs showed appreciable improvement. Admitted to sanatorium where he was treated until Oct. 1949. *X-ray of lungs* (Oct. 1949): Both lungs show increased opacity round the cardiac shadow taking the form of fine flecks. This is most marked on

the right side. Large dense hilar shadows without the outline of nodes. During his stay in the sanatorium the patient developed pleuritis and tuberculous osteochondritis of a rib.

Case 22. ♀, born 1906. Treated in hospital in 1947 under the diagnosis hepatitis. No heredity for tuberculosis. Became ill in July 1947 with slight fever, sharp pains in the upper part of the abdomen and general malaise. Had similar symptoms in Aug. of the same year and was admitted to hospital. *On admission:* General condition relatively good. Slight icterus. *Meulengracht:* 44. *Abdomen:* Soft, not tender. The liver is palpable two fingers breadths below the costal margin. *Takata:* Positive. Urobilin + + +. An exploratory laparotomy was performed. The enlarged liver was felt firmer than normal. The gall bladder and bile duct were free of stones. There were a number of enlarged lymph nodes along the upper border of the pancreas. The spleen was more than twice the normal size. A piece of liver and a lymph node were taken for biopsy. *Microscopic examination U. 5440/47* (Prof. Gellerstedt): There is no true cirrhosis of the liver but a definite and widespread chronic inflammatory reaction in the increased periportal connective tissue. There are occasional small collections of epithelioid cells and giant cells in this region but, without any caseation. There are similar granulomatous foci in the lymph nodes. They take the form of a dense sprinkling of submiliary foci but here again there is no caseation. The picture is somewhat reminiscent of that seen in the lymph nodes in Schaumann's disease. *Patho-anatomical diagnosis:* Chronic hepatitis + atypical tuberculosis of the lymph nodes. — After operation the patient was transferred to the medical department. *Superficial lymph nodes:* No enlargement. *X-ray of lungs:* Negative. *X-ray of bones of hand.* No abnormality. *Mantoux:* 3 mg negative. *Blood:* Slight anemia, otherwise no abnormality. *Follow up* (May 1948): *X-ray of lungs:* No abnormality. *SR:* 42 mm/hr.

Case 23. ♂, born 1913. One of the patient's aunts had had pulmonary tuberculosis. The patient went to a physician on account of swelling of the lymph nodes of the neck. General condition good. *Superficial lymph nodes:* Rather hard lymph nodes about the size of walnuts behind both angles of the jaw. Another the size of an almond below the left margin of the jaw. All freely mobile. No other palpable nodes. *SR:* 23 mm/hr. *Mantoux:* 1 mg negative. *Blood:* No abnormality. Removal of a lymph node. *Microscopic examination S. 977/48* (F. Wahlgren, M.D.): The lymph node is tightly packed with small rounded groups of epithelioid cells. There are occasional giant cells of the Langhans type, also a trace of caseous necrosis. The microscopical picture suggests that this is a case of lymphogranuloma benignum. *Patho-anatomical diagnosis:* Probably lymphogranuloma benignum, possibly tuberculosis. — Felt tired and apathetic towards the end of 1950. Pains in the chest on deep breathing. Examined as an out-patient in Jan. 1951 when a pleuropneumonic affection of the left lung was diagnosed. Admitted to hospital where he was treated under the diagnosis of Schaumann's disease. *X-ray of lungs* (in Jan. 1951): There is enlargement and increased density of both hilar regions. Thin pleural shadow along the left lateral wall of the thorax with a fairly broad interlobar line running inwards towards the hilus. Coarse linear markings in the upper part of the left lung. X-ray examination thus shows the presence of a pleuroparenchymatous process in the left lung. This may be specific. *Re-examination of lungs* (a week later): The opacity in the left second intercostal space is still there unchanged. There has appeared a faint cloudy opacity, barely the size of the tip of a thumb in the lateral part of the left first intercostal space and behind the second rib. *X-ray of bones of hands:* No abnormality. *X-ray of lungs* (30.3. 1951): Quite considerable regression of both the pleural and parenchymatous shadow in the left lung. The hilar opacity remains as before. The patient was afebrile throughout the illness. *SR:* About 50 mm/hr. *WBC:* About 10,000/mm^3. *Mantoux:* 1 mg negative. At follow up in March 1951 the SR was 10 mm/hr.

Case 24. ♂, born 1909. Treated in hospital in 1948. No heredity for tuberculosis. In April 1948 swelling of the ankles and fever, about 39° C. Afebrile after one month. In May eye symptoms. They consisted in impairment of vision and pain. By the middle of May the swelling of the ankles had disappeared, but at this time both parotid glands swelled. *On admission:– Superficial lymph nodes:* No abnormality. *Salivary glands:* Slight enlargement of the parotid glands on both sides. *Joints:* No abnormality. *X-ray of lungs:* Multilobular mass of lymph nodes in both hili. *Ophthalmological investigation:* Iridocyclitis acuta. *X-ray of bones of hands and feet:* No abnormality. *Guinea pig test and culture of Loewenstein's medium:* Negative, using gastric lavage fluid. Extirpation of a lymph node. *Microscopic examination V. 1627/48* (I. Behring, M.D.): The lymph node is thickly studded with foci of epithelioid cells with giant cells. No signs of necrosis. This is most probably a case of Schaumann's disease. — *X-ray of lungs* (July 1948): Great enlargement of the lymph nodes in the hilar regions. Fine linear markings in both lung fields. — In Dec. 1948 the parenchymatous lesions were found to have progressed.

Case 25. ♂, born 1913. Treated in hospital in 1948 under the diagnosis of acute iritis (Schaumann's disease). No heredity for tuberculosis. In 1943 the patient's sister was treated for l. b. The patient was in contact with her for a couple of short periods during that time. Became ill in June 1948 with symptoms of both eyes. These consisted of redness, pain and photophobia. *Ophthalmological examination* (July 1948): Iritis acuta. — *X-ray of lungs:* Bilateral enlargement of the hilar nodes. Biopsy of a lymph node. *Microscopic examination V. 1832/48* (author): The lymph node, which is about the size of a haricot bean, is fairly sparsely studded with miliary-submiliary foci of epithelioid cells with some admixture of giant cells of the Langhans type. There is also a certain amount of sclerosis of the basal reticulum of the tissue and an absence of any noteworthy amount of perifocal lymphocytic reaction. No caseation anywhere. The picture thus corresponds with that seen in *lymphogranulomatosis benigna.* — *Fractional serum protein analysis:* Total protein 7.1 %, albumin 3.3 %, globulin 3.8 %. A/G 0.9. — *Mantoux:* 1 mg positive. *Guinea pig test and culture* with gastric lavage fluids were negative. The lesions of the eyes had practically disappeared by the end of Sept. 1948. There was no palpable enlargement of the lymph nodes. *Blood:* No abnormality. *SR:* Remained 3–9 mm/hr. throughout the course of the illness. *X-ray of bones of hands and feet:* No abnormality.

Case 26. ♂, born 1919. Treated in hospital in 1948 under the diagnosis of Schaumann's disease. No heredity for or known contact with tuberculosis. 1945 suffered from acute bilateral iridocyclitis. In 1948 marked enlargement of the lymph nodes of the neck was noticed. *On admission* (1948): General condition satisfactory. *Superficial lymph nodes:* There are numerous lymph nodes adherent to one another ranging in size from that of a grain of wheat to that of a walnut on both sides of the neck in the submandibular region, over the mastoid process, lateral to the posterior border of the sternocleidomastoid and in the supraclavicular fossae. No palpable nodes in the axillae or groins. Removal of a node. *Microscopic examination S. 2508/48* (Å. Lindgren, M.D.): A node the size of a cherry very thickly studded with small epithelioid cell tubercles. Here and there the tubercles are confluent. Occasional giant cells. No caseous necrosis. Staining for tubercle bacilli gave negative results. *Patho-anatomical diagnosis:* Schaumann's disease. — *SR:* 49–70 mm/hr. *Mantoux:* 0.1 mg negative. *WBC:* 6,800/mm³. Eosinophils 3 %, monocytes 19 %. The patient attended hospital for the following two years for observation. Joint pains from time to time, sometimes in the left hip and sometimes in the back, also muscular pains. In June 1950 the SR was 37 mm/hr.

Case 27. ♂, born 1922. Treated in a military hospital in 1948 and 1951 under the diagnosis of lymphogranulomatosis benigna, also in a county hospital in 1948

under the same diagnosis. No heredity for tuberculosis. Became ill in Feb. 1948 with symptoms resembling those of influenza and did not fully regain his health; therefore, in Feb. 1948, his lungs were X-rayed and "opacities suggestive of tuberculosis" were found in the parenchyma. The tuberculin reaction was, however negative. No tubercle bacilli in the sputum, although repeated searches were made. *X-ray of lungs* (in May 1948): There is a fairly diffuse scattering of opacities up to the size of peas throughout the parenchyma of both lungs. On the right side they are confluent and form an opacity which occupies the greater part of the superior lobe. No definite enlargement of the hili. Diagnosis: Probably Schaumann's disease. — *SR:* 23 mm/hr. Normal blood picture. *Mantoux:* 1 mg negative. Afebrile. While in hospital in 1948 there was swelling beneath the mandible on the right side on two occasions. It only lasted for a short time. *X-ray of bones of hands and feet:* No abnormality. — Towards the end of 1948 there was pain on swallowing under the right side of the mandible. During the last weeks swelling there. Visited the county hospital where a mass barely the size of a walnut was found below the mandible on the right side. It had a firm consistency and was fixed to the surrounding tissues but was not tender. It was removed. *Microscopic examination U. 8038/48* (Prof. Gellerstedt): Atypical tuberculosis in the form of scattered submiliary tubercles without caseation and with the characteristic type of giant cells. *Patho-anatomical diagnosis:* Schaumann's disease. — Transferred to The Radium Hospital in Stockholm for radiotherapy. In the spring of 1951 the urine gave a positive Heller reaction so that he was again admitted to the military hospital. Albuminuria 0.3 %. Some red cells in the sediment. *Non-protein serum nitrogen:* 37 mg %. *Repeat X-ray of bones of hands and feet:* No abnormality. *X-ray of lungs:* Considerable regression of the pulmonary lesions. *Serum calcium:* 9.5 mg %. *AST:* 90 units/ml.

Case 28. ♀, born 1907. Husband died of tuberculosis in 1933. One son had "nodes on the lungs". — Diabetes since 1929. 1934–1945 treated in hospital for tuberculosis of the right lung. 1949 chronic tonsillitis + acute nephritis. Albuminuria since then. Suffered from progressive lassitude and loss of weight in the spring of 1949. Treated in hospital for hilar tuberculosis, also in another hospital during the same year under the diagnoses of lymphogranuloma benignum + chronic nephritis + diabetes mellitus. Relatively large and firm bundles of nodes were discovered and one was removed for biopsy. *Microscopic examination Umeå 1633/49* (Dr. C. W. Lundqvist): The lymph node from the right axilla shows the picture of a chronic lymphadenitis in the form of so-called "sinus catarrh" but also is scattered with numerous epithelioid cell tubercles with giant cells of both the Langhans and the foreign body type. No foreign bodies were, however, seen. *Patho-anatomical diagnosis:* Tuberculous lymphadenitis. *Mantoux:* 1 mg negative. *SR:* 56–69 mm/hr. *Blood:* Eosinophils 5 %. — Heller: +, Esbach 1,2–2 ‰. Non protein serum nitrogen: 65 mg %. *X-ray of lungs:* Both hili show large lobulated shadows. — *X-ray of hands:* No Jüngling's osteitis. — There was long-standing conjunctivitis which gradually regressed. Readmitted to hospital in 1950 under the diagnosis lymphogranulomatosis benigna + diabetes mellitus + nephritis. *On admission:* General condition not good. Slight oedema of the lower leg. *Heart:* Sounds somewhat blurred. *Blood pressure:* 195/110. *Lungs:* Loose râles over the bases. *Abdomen:* No abnormality. — Slight fever from time to time. *SR:* 76–112–40 mm/hr. Heller: +, Esbach: 8 ‰. Non protein serum nitrogen. 33 mg %. *Blood:* Slight anemia. *WBC:* 3,700/mm³. Eosinophils 3 %. *Serum protein:* 7,1 mg %. Albumin 2.5 %, globulin 4.6 %. A/G 0.5. *Sternal puncture:* No specific characteristics. Extirpation of a lymph node. *Microscopic examination S. 3363/50* (F. Wahlgren, M.D.): The lymph node contains large numbers of masses of epithelioid cells which show no tendency to caseous necrosis. These foci of epithelioid cells often contain one or more giant cells of the Langhans' type. The microscopical picture is reasonably characteristic of lymphogranulomatosis benigna although the number of giant

cells in unusually large. *Patho-anatomical diagnosis:* Schaumann's disease. — *Guinea pig test* (with gastric lavage fluid): Negative. *Mantoux:* Negative. *X-ray of lungs:* The enlargement of the hilus is somewhat less marked than on the occasion of the last radiograph. — Discharged in relatively good condition. — Readmitted to hospital in 1951. Her general condition had remained good since her discharge in 1950. Suddenly became ill three weeks before admission with breathlessness and pain in the chest. Temp. 38° C. *General condition:* Rather poor condition. In May 1951 a lymph node was removed for biopsy. *Microscopic examination* Umeå 1844/51 (Dr. C. W. Lundqvist): The lymph node shows scattered groups of epithelioid cells, varying in size, with Langhans' giant cells and sometimes central caseous necroses. *Patho-anatomical diagnosis:* Tuberculous lymphadenitis. — The patient grew steadily worse and died in the middle of August 1951. No tubercle bacilli were demonstrated in sputum during the whole course of the illness. *Culture and guinea pig test* as late as July 1951 gave negative results. *Partial autopsy:* There was a relatively large quantity of clear yellow fluid in the abdominal cavity. No fluid in the pleural cavities. The *left lung* showed no abnormality. The *right lung* was completely adherent to the chest wall. Section through the right lung showed several areas of whitish grey infiltration varying in size and showing no liquefaction. The section also passed through a capsulated space between the middle and lower lobes of the right lung. It was the size of a fist and filled with clear, yellow fluid. The pericardium contained about 250 cc of clear yellow fluid. The *heart* seemed abnormally firm with definite enlargement of the left side. None of the heart valves showed any lesion. No thrombi or emboli were to be seen. The pulmonary artery was opened and showed no abnormality. The left ventricle was hypertrophied and its wall was about 3 cm think. Section of the heart muscle showed several fibrotic foci. The coronary vessels showed no abnormality. *Spleen:* No abnormality. *Liver:* Signs of stasis but no other abnormality. *Kidneys:* Capsule stripped easily on both sides. The surface seemed unusually greyish white and the cortex was rather thin. *Lymph nodes:* A large bundle of lymph nodes was excised from the right axilla, some of the nodes were as large as walnuts. The bundle broke and a large amount of greenish yellow pus ran out. — The lymph nodes and the lungs were sent to the Pathological Institute in Uppsala. *Microscopic examination* U.B.E./51 (author): Submiliary epithelioid cell foci, some of them containing Langhans' giant cells, are sparsely scattered through the lungs. Some of the giant cells contain asteroid bodies. There is no caseous necrosis anywhere. The tubercles are chiefly to be found in the peribronchial regions. The hilar lymph nodes contain numerous rounded foci consisting of hyaline connective tissue with few cells. The lymph nodes from the axilla show the picture of caseous tuberculosis. Acid-fast rods present. *Patho-anatomical diagnosis:* Lymphogranulomatosis benigna of both lungs and the hilar lymph nodes + caseous tuberculous lymphadenitis of the right axilla.

Case 29. ♂, born 1915. No heredity for tuberculosis but had been in contact with persons suffering from tuberculosis about 12 years ago. Had erythema nodosum in May 1949. *X-ray of lungs* (July 1949): Limited enlargement of the hilar nodes on the right side. *X-ray of lungs* (Aug. 1949): Bilateral hilar enlargement. Repeated *Mantoux tests* during Aug.-Dec. 1949 gave negative results. In May 1949 the patient slipped in a foundry and scraped a piece of skin off the dorsal surface of the right middle finger. The wound healed in a week but then broke down and grew larger. In the beginning of August the patient developed a sore on another finger where he had for a long time had a well healed scar. Another little sore appeared a week later, this time on the under surface of the arm just below the elbow. In Aug. a piece of the sore on the right middle finger was taken for biopsy. *Microscopic examination U. 6794/49* (Prof. Fåhræus): The edge of the wound contains masses of typical tubercles and caseous necroses. No doubly refractive material. No tubercle bacilli could be found. *Patho-anatomical diagnosis:* Tuber-

culosis. — In the middle of Sept. 1949 two nodes in the right cubital fossa had become enlarged. One was removed. *Microscopic examination S. 2944/49* (F. Wahlgren, M.D.): The lymph node, which was about the size of an almond is tightly packed with tubercle-like groups of epithelioid cells. Occasional tubercles contain giant cells of the Langhans type. In some places there are the beginnings of caseous necrosis while in others there are the beginnings of fibrous induration. Tubercle bacilli were not demonstrated in the section. The microscopic picture suggests that this is a case either of tuberculosis or lymphogranuloma benignum but is really more like the picture seen in the latter condition. — In Oct. 1949 a further piece from the sore on the right middle finger was taken for biopsy. *Microscopic examination U. 8511/49* (S. Ranström, M.D.): The small piece of material contains large amounts of tuberculous granulomatous tissue. No doubly refractive material. *Patho-anatomical diagnosis.* Tuberculosis. — *SR* in Aug. was 36 mm/hr. but was normal in Nov.–Dec. *WR:* negative. Treated with streptomycin and PAS and discharged cured in the middle of Jan. 1950. — The author re-examined both preparation U. 6794/49 and U. 8511/49 to make sure whether there were any acid-fast rods present. In spite of careful searches none were to be found. There was no doubly refractive material in the tissues.

Case 30. ♂, born 1892. Treated in hospital in 1949 under the diagnosis of Schaumann's disease. In 1940 right sided iridocyclitis and, at about the same time, rheumatic fever. On examination as an out-patient in 1949 the patient mentioned that for about the past ten years he had noticed swelling of one toe on each foot and for the past 3 years had pain in one finger. He had also noticed swollen nodes in his neck for several years. Also for several years he had had a redness of the skin in one temporal region. On *admission:* General condition satisfactory. *Superficial lymph nodes:* On each side of the neck there were about ten lymph nodes ranging in size from that of a grain of wheat to that of a pea. In the axillae they were up to the size of chestnuts and in the groins up to the size of almonds. *Heart:* Systolic and diastolic blowing sounds. *Skeleton:* Severe dorsiflexion of the third right toe and the second left toe and of the right index finger. — The right index finger was amputated. *Microscopic examination* (F. Wahlgren, M.D.): *Patho-anatomical diagnosis:* Lymphogranuloma benignum. — Removal of a lymph node from the neck. *Microscopic examination S. 3586/49* (F. Wahlgren, M.D.): The lymph node shows marked changes and contains many rather irregular foci of the nature of epithelioid cell tubercles. Giant cells of the Langhans type are occasionally to be seen in these foci. There is no significant tendency to caseous necrosis. Fresh formation of collagen fibrils is seen in association with the formation of the tubercles. Here and there in the tissue there may be seen quite broad strips of connective tissue. The microscopic structure is of the sort commonly seen in Schaumann's disease. — *X-ray of lungs:* Increased fuzzy markings in the middle part of the right lung field. *Mantoux:* 1 mg negative. *Blood:* Eosinophils 4 %, monocytes 12.5 %. *SR:* 15 mm/hr.

Case 31. ♂, born 1927. Treated in hospital in 1949 under the diagnosis of lymphogranulomatosis benigna. No heredity for or known exposure to tuberculosis. *X-ray of lungs* in 1947 on starting military service showed no abnormality. Had BCG vaccination in Feb. 1946 and June 1947 with negative results both times. Noticed shortness of breadth on effort since the beginning of March 1949. At the same time developed a cough with mucous sputum. Feeling of dryness in the mouth and pain across the chest. In April 1949 the "glands inside the neck" swelled so that the patient was hoarse for a time. In the beginning of May 1949 there were palpably enlarged lymph nodes in the neck. *On admission:* General condition good, no fever. *SR:* 20 mm/hr. *Superficial lymph nodes:* There is a firm lymph node the size of a bean in each axilla, also smaller ones in the cubital fossae. Behind the mandible on each side there is a bundle about the size of a plum con-

sisting of lymph nodes adherent to one another. In the supraclavicular fossa is a hard node the size of a pea and in the right groin several more relatively firm painless nodes about the size of beans. *WBC:* 7,600/mm³. Removal of a cubital lymph node. *Microscopic examination U. 3992/49* (Prof. Gellerstedt): The whole node is densely infiltrated with submiliary epithelioid cell tubercles some of which are confluent. There is no significant caseous necrosis and very few giant cells. If the clinical picture suggests Schaumann's disease the microscopical findings support this suggestion. *Patho-anatomical diagnosis:* Atypical tuberculosis. — *Mantoux:* 0.1 mg negative. *X-ray of lungs:* Both hili greatly enlarged. Fine mottling in the lung fields, especially the bases. *X-ray of skeleton:* No abnormality. *Ophthalmological examination:* No abnormality.

Case 32. ♀, born 1899. Treated in hospital in 1949 under the diagnosis of Schaumann's disease. In 1948 the patient noticed swelling under the eyes and over both parotid glands. *On admission:* General condition satisfactory. *Superficial lymph nodes:* There are several smaller lymph nodes on the right side of the neck. Biopsy. *Microscopic examination U. 4165/49* (Prof. Gellerstedt): Dense infiltration of the node with small epithelioid cell tubercles without caseous necrosis. Looks like *Schaumann's disease.* — *X-ray of lungs:* No lesions. *X-ray of bones of hands and feet:* No lesions typical of Schaumann's disease. *WBC:* 3,600/mm³. *SR:* 13–30 mm/hr. *Mantoux:* 1 mg negative.

Case 33. ♀, born 1885. Treated in hospital in 1950 under the diagnosis oedema of the lungs. Had had "asthma" with severe breathlessness on exertion for many years. *On admission:* General condition very poor. Severe dyspnoea and cyanosis. Oedema of arms and legs. *Lungs:* Many loose râles and tracheal adventitious sounds. In spite of intensive treatment with strophanthin, oxygen etc. the patient died a couple of hours after admission. *Autopsy U. 397/50* (author): *Central nervous system:* No abnormality. *Respiratory organs:* The right lung is attached to the chest wall over the greater part of its surface by fibrous adhesions. The left only slightly so. The trachea and larger bronchi contain large amounts of froth. Alongside the trachea there are many firm lymph nodes. They range in size up to that of a hazel nut and the cut surfaces are greyish without caseous change. There are many flat, rather firm, greyish yellow nodules about the size of a split pea on the surface of the right lung. Section of the lung shows streaks of fibrous tissue radiating from the hilar region interspersed with firm, yellowish grey, rounded foci about the size of half a pea. In one of the lungs there are two cavities the size of peas in the dense fibrous tissue. The walls of these spaces are anthracotic. Nowhere is there any sign of caseation. There is also emphysema and bronchiectasis. The hilar lymph nodes are barely the size of hazel nuts, considerably firmer than normal and greyish yellow on the cut surfaces. At the bifurcation of the trachea there is a bundle about the size of a walnut made up of several similar-looking nodes. Nowhere is there any caseation. *Organs of circulation:* The heart presents the picture associated with chronic pulmonary insufficiency. Opening of the pulmonary artery shows that the intrapulmonary vessels are lined with a greyish white material in several places. *Abdominal organs:* The liver shows no significant change. There are a couple of soft yellowish lymph nodes about the size of haricots in the portal region. The spleen is of normal size and shows no definite changes. There is a calcified lymph node in the mesentery of the small intestine. Along the course of the abdominal aorta there are several lymph nodes the size of hazel nuts. *Superficial lymph nodes:* The nodes of the lateral parts of the neck and of the groins are moderately enlarged. Those in the axillae are not enlarged. *Microscopic examination* (author): There is considerable fibrosis of the *lungs* which are rather densely sprinkled with miliary, often confluent, tuberculoid foci composed of epithelioid cells and numerous Langhans' giant cells. Some of the giant cells contain asteroid bodies. Considerable fibrous induration of the granulomata. In

several places the granulomatous process is seen to be affecting the walls of the blood vessels. In some places the vessels are destroyed and the walls full of granulomatous tissue of specific character (Figs. 48, 49). The pulmonary artery contains a few isolated endothelially situated epithelioid cell granulomata with giant cells (Figs. 50, 51). The *liver* shows no noteworthy change. The *spleen* contains many more or less fibrotic submiliary epithelioid cell granulomata, mostly associated with the arteries. No noteworthy changes in either the *kidneys* of *suprenal bodies. Heart muscle:* No abnormality. The paratracheal and hilar *lymph nodes* contain large fibro-hyaline masses as well as epithelioid cell granulomata without caseous necrosis. Even in the mesenteric and para-aortic nodes there is a dense infiltration of miliary epithelioid cell granulomata with a considerable tendency to fibrous induration. Nowhere is there any tendency to caseous necrosis. The lymph nodes from the groins show no noteworthy changes. *Patho-anatomical diagnosis:* Lymphogranulomatosis benigna.

Case 34. ♀, born 1917. Treated in hospital in 1950 under the diagnosis tuberculous lymphadenitis and in a sanatorium in the same year under the diagnosis of sarcoidosis. No heredity for or known exposure to tuberculosis. Never had erythema nodosum, pleurisy or pneumonia. Tendency to sore throats. Swelling of the lymph nodes of both sides of the neck set in suddenly in the middle of Dec. 1950 and increased rapidly. No fever. Went to a physician in Feb. 1951 on account of the lymph node disease and of inflammation in the left eye (conjunctivitis?). *Lymph nodes:* Fairly widespread enlargement. *WBC:* 3,400/mm³. *Mantoux:* 0.1 mg negative. *X-ray of lungs:* The hilar contours are of about the normal size. Somewhat increased diffuse markings in the parenchyma. — Extirpation of a lymph node from the neck. *Microscopic examination S. 1042/50* (A. Bergstrand, M.D.): The lymph node is completely filled with numerous groups of epithelioid cells, sometimes confluent, containing giant cells of the Langhans type. Central necrosis. *Patho-anatomical diagnosis:* Tuberculosis. — The patient received radiotherapy in the course of which the nodes diminished in size. In Aug. 1950 there was an illness with an acute onset with chills and the temperature stayed up to 40° C for about a week. Admitted to a sanatorium. *On admission:* General condition not very good. *Superficial lymph nodes:* Generalised enlargement. The nodes are up to the size of beans. *X-ray of lungs:* The hilar shadows are enlarged. There are small opacities scattered throughout the parenchyma (Fig. 27). *Mantoux:* 3 mg negative. *SR:* 18–42 mm/hr. *WBC:* 4,000/mm³. Eosinophils 5–10%, monocytes about 10%. *AST:* 100 units/ml. *ASTA:* 1.6 units/ml. *Bones of hands and feet:* No abnormality. Repeat extirpation of a node. *Microscopic examination S. 3534/50* (F. Wahlgren, M.D.): The lymph node examined this time is tightly packed with tubercle-like groups of epithelioid cells some of which contain giant cells of the Langhans type. Occasionally one of these groups of cells shows a tendency to central caseous necrosis. There is, however, a considerable tendency to fibrous induration. Tubercle bacilli were not demonstrated in the sections. The microscopical picture may be said to be fairly typical of that seen in lymphogranuloma benignum. — In view of this diagnosis the lymph node which had previously been sent in was re-examined (F. Wahlgren, M.D.). A similar picture was found in it. The epithelioid cell groups were, however, larger there and showed a marked tendency to caseous necrosis. There was, however no tendency to fibrous induration. Tubercle bacilli could not be demonstrated. It may thus be said that this first node presents a picture very like that seen in tuberculosis, but, in view of the later development of the case, the condition is probably the same as that which prevailed in the node which was sent in later.

Case 35. ♀, born 1913. No heredity for tuberculosis. Erythema nodosum 1929. Treated in hospital in 1946 for uveoparotid fever. At that time Mantoux positive for 0.01 mg. *X-ray of the lungs:* Enlarged lymph nodes in the left hilus. The uveitis

healed in 7 months. After this healthy until Christmas time 1949 when she noticed a couple of small lymph nodes on the left side of the neck. *X-ray of the lungs* (March 1950): Fine speckling in the central parts of both lung fields. *Mantoux:* Now negative for 0.01 mg but positive for 0.1 mg. Biopsy of a lymph node. *Microscopic examination V. 1360/50* (I. Behring, M.D.): The lymph node shows foci of epithelioid and giant cells closely packed in fibrous and hyaline masses of connective tissue. No trace of caseous necrosis. The original lymphoid tissue has been completely destroyed. *Patho-anatomical diagnosis:* Schaumann's disease. *SR:* 5–15 mm/hr. *X-ray of bones of hands and feet:* No abnormality. *Ophthalmological examination:* No abnormality. *Guinea pig test and culture:* No tubercle bacilli using gastric lavage fluid. Repeat radiographs of the lungs on several occasions during 1950–52 showed no change.

Case 36. ♀, born 1901. Treated in hospital in 1950 under the diagnosis of lymphogranulomatosis benigna. Had noticed marked enlargement of the parotid glands on both sides for the past two months. At the same time had suffered from a cold in the head and cough. *On admission:* There is a fairly firm tumour in the position of the left parotid gland which extends downwards towards the angle of the jaw. Below it there are a couple of hard masses the size of haricots. The findings on the right side are similar. *X-ray of lungs:* Increased markings in both lung fields. *X-ray of bones of hands and feet:* An area of rarefaction about the size of a grain of rice. *SR:* About 37 mm/hr. *Blood:* Anemia, otherwise no abnormality. *WR:* Negative. *Mantoux:* 0.1 mg positive. Extirpation of a lymph node. *Microscopic examination U. 3543/50* (S. Ranström, M.D.): The lymph node is infiltrated with typical epithelioid cell tubercles with a definite tendency to induration round each tubercle. A few small necroses. There is nothing in the picture to contradict the suggestion that this is a case of lymphogranulomatosis benigna. *Patho-anatomical diagnosis:* Atypical tuberculosis.

Case 37. ♀, born 1922. Treated in hospital in 1952 under the diagnosis of chronic rheumatic endocarditis with heart failure + lymphogranulomatosis benigna. In 1932 had rheumatic fever with joint pains and pericarditis. High fever. In 1934 a recurrence of the pericarditis. In the spring of 1950 the patient noticed tender lumps on either side of the neck above the clavicle. In Nov. 1950 one was removed. *Microscopic examination S. 4494/50* (F. Wahlgren, M.D.): The normal structure of the lymph node is destroyed. It contains a very large number of tubercle-like foci of rather variable size lying close to one another. They are composed of epithelioid cells and here and there contain giant cells some of which have their nuclei round the periphery while in others they are scattered throughout the cell. There is no tendency to necrosis. The tissue between these foci is largely occupied by new formation of collagen connective tissue. Acid-fast bacilli were not seen. The histological picture suggests this is a case of lymphogranulomatosis benigna. — As a result of this patho-anatomical diagnosis the lungs were X-rayed and showed a picture typical of *Schaumann's disease.* There is no information as to the tuberculin reaction. — In March 1952 a sudden attack of paroxysmal tachycardia led to severe decompensation of the heart. *SR:* Normal. *Blood:* No changes of interest. — The patient's condition became worse and in June 1952 she died. *Autopsy* (F. Wahlgren, M.D.): Chronic, recurrent, severe endocarditis with enlargement of the heart and thromboses in the auricles. The serous surface of the lungs showed a "quite peculiar" net-like marking but no definite lesions of the parenchyma. Around the hilar regions and in the posterior mediastinum were some soft greyish brown or grey lymph nodes the largest of which were the size of almonds. The spleen weighed 180 g. On the cut surface there were scattered a large number of greyish white nodules, mostly about the size of a pin's head. In some places these were confluent and formed aggregates as large as a pea which were raised above the level of the cut surface. Microscopical examination gave the diagnosis of *lymphogranulomatosis benigna.*

Case 38. ♂, born 1921. Treated in hospital in 1950 under the diagnosis of Schaumann's disease. No heredity for or known exposure to tuberculosis. Erythema nodosum in Feb. 1950. After that unduly tired. In April 1950 a recurrence of the erythema nodosum. *Mantoux:* 1 mg negative in the middle of May. *On admission* (in July 1950): *Superficial lymph nodes:* No abnormality. *Heart:* Soft systolic murmur over the whole heart. *Abdomen:* No abnormality. *Blood:* Eosinophils 3–11 %. *SR:* 3–5 mm/hr. *WR:* Negative. *X-ray of lungs:* Considerable enlargement of the hili with enlarged lymph nodes. The parenchyma shows a fine mottling on both sides. Extirpation of a lymph node from the groin. *Microscopic examination U. 5927/50* (S. Ranström, M.D.): The lymph node is infiltrated with epithelioid cell tubercles lying close to one another and there is a tendency to induration. Few giant cells, no necroses. *Patho-anatomical diagnosis:* Lymphogranulomatosis benigna.

Case 39. ♂, born 1889. Treated in hospital in 1946 under the diagnosis of presenility + cardiosclerosis and again in 1950 under the diagnosis of presenility + lymphogranulomatosis benigna. No heredity for or known contact with tuberculosis. Previously always in good health apart from some trouble with the urinary tract in 1941 (stone?). In 1944 a dull ache in the region of the heart. Pain on exertion. Marked tiredness. In 1946 increasing shortness of breadth, palpitation and a sensation of pressure over the chest. Admitted to hospital in 1946 for investigation in connection with a pension. *On admission:* General condition satisfactory. No cyanosis or oedema. *Superficial lymph nodes:* In the left groin there are a couple of nodes the size of a pea. *Mantoux:* 1 mg negative. *WBC:* 7,200/mm³. *SR:* 31 mm/hr. Investigation of the heart showed no definite lesion. The breathlessness increased steadily after discharge in 1946. Admitted in 1950 for investigation of the cause of the breathlessness. *On admission:* General condition satisfactory. *Superficial lymph nodes:* A few the size of grains of wheat in front of and behind each sternocleidomastoid. 3–4 the size of peas or beans in each axilla, those in the left axilla being adherent to one another. *Abdomen:* No abnormality. *X-ray of lungs:* Marked emphysema with large cavities and fine mottled marking extending diffusely throughout both lungs. There is probably a diffuse interstitial indurative process at work in this case. The picture is reminiscent of a coniosis. — Re-examination of the plates from 1946 showed that there was already a suspicion of lesion similar to those now to be seen. As the pulmonary lesions were suspected of being due to a pneumoconiosis the history of the patient's employment was gone into in more detail. It then turned out that he had worked as a stone breaker for 3–4 months each year during the years 1939–43. — Extirpation of a lymph node. *Microscopic examination U. 6283/50* (S. Ranström, M.D.): Slight diffuse fibrosis of the tissue of the lymph node with a scattering of epithelioid cell tubercles containing some giant cells. The picture corresponds with that seen in lymphogranulomatosis benigna. *Patho-anatomical diagnosis:* Lymphogranulomatosis benigna. *Mantoux:* 3 mg negative.

Case 40. ♂, born 1894. Treated several times in hospital under the diagnosis lymphogranulomatosis benigna + thrombocytopenic purpura. No heredity for or known exposure to tuberculosis. In 1950 punctate red flecks on the skin, most numerous over the hips and legs. Attended the out-patient department of the hospital for this reason and was admitted for investigation of the hemorrhagic tendency. *On admission:* General condition satisfactory. Afebrile. Numerous petechiae, especially on the hips and legs. *Superficial lymph nodes:* No abnormality. *X-ray of lungs:* Immediately behind and below the left hilus there is a thin infiltration about the size of a plum. Both hili are denser and larger than normal, especially the right, which shows a convex and markedly lobulated contour towards the lungs (enlarged lymph nodes). *SR:* 55–75 mm/hr. *WBC:* 3,200–6,900/mm³. Eosinophils 5–8 %, monocytes 9–13 %. Thrombocytes 35,000–50,000/mm³. (Kri-

stensson's method, normal value 200,000–400,000/mm³.) The appearance of the pulmonary lesions and the fact that the patient proved tuberculin negative using up to 10 mg tuberculin led to extirpation of a lymph node the size of a bean from the right groin. *Microscopic examination U. 7939/50* (Prof. Fåhræus): The lymph node is completely packed with typical giant cell tubercles. Practically no caseation. *Patho-anatomical diagnosis:* Tuberculous lymphadenitis. *X-ray of bones of hands and feet:* No abnormality. *X-ray of spleen:* No enlargement. — The patient was treated with PAS during which treatment the infiltration in the left lung practically disappeared. When the treatment had ceased a relatively thin infiltration reappeared below the hilus. Some months later (March 1951) a number of small opacities were found in the right lung as well at the level of the hilus. *Ophthalmological examination:* No abnormality. *Culture on Loewenstein's medium:* Negative on two occasions using gastric lavage fluid. In March 1951 repeat biopsy of a lymph node, this time from the left groin. *Microscopic examination U. 2173/51* (Prof. Gellerstedt): The lymph node is tightly packed with small tubercles. Little necrosis, slight tendency to sclerosis. Fairly typical "Schaumann picture". *Patho-anatomical diagnosis:* Atypical tuberculosis. *X-ray of lungs* (June 1951): No definite change in condition since March 1951. *Mantoux:* 3 mg negative.

Case 41. ♂, born 1912. Treated in hospital in 1950 under the diagnosis of lymphogranulomatosis benigna. 16 years before had been working with a man who fell ill with tuberculosis and was admitted to a sanatorium. No heredity for or other known exposure to tuberculosis. For the past 10 years had suffered from abdominal trouble resembling gastritis. The reason for admitting the patient to hospital was that screening of the lungs had shown suspicious changes. *On admission:* General condition good. Afebrile. *Superficial lymph nodes:* Some about the size of grains of wheat behind the sternocleidomastoid and one about the size of a bean in the left axilla. *Abdomen:* No abnormal mass palpable. *SR:* 13 mm/hr. *WBC:* 4,800, 6,600/mm³. Eosinophils 2%, monocytes 11%. *Fractional serum protein analysis:* Total protein 8.2%, albumin 4.3%, globulin 3.9%. A/G 1.1. *Mantoux:* 3 mg negative. *X-ray of lungs:* There are opacities of various sizes diffusely scattered through the upper half of the right lung and the upper two thirds of the left lung. They are mostly small but on a level with the left hilus there are some as large as peas. The hili are of normal size. The nature of the process is not obvious. — Excision of a lymph node from the left axilla. *Microscopic examination U. 8343/50* (S. Ranström, M.D.): The lymph node is filled with epithelioid cell tubercles. There are practically no necroses. Considerable tendency to induration. The picture is consistent with lymphogranulomatosis benigna. *Patho-anatomical diagnosis:* Atypical tuberculosis. *Culture on Loewenstein's medium:* Negative using gastric lavage fluid. *X-ray of lungs* (Dec. 1950): For the most part no change.

Case 42. ♀, Treated in hospital in 1949 under the diagnosis Schaumann's disease, rheumatic fever?, in 1950 under the diagnosis cholelithiasis + chronic cholecystitis + Schaumann's diesase, and later in the same year under the diagnosis of Schaumann's disease. No case of tuberculosis in the family. Became ill at Christmas time in 1947 with stiffness of the neck and slight difficulty in walking. Later had a red rash over the whole body which, in places was clearly typical erythema nodosum. At the same time hilar adenitis, swelling of the joints and eye changes of doubtful nature (tuberculosis? Schaumann's disease? rheumatism?). Swelling of the lymph nodes of the neck and right axilla developed gradually. Also further skin lesions on the face. Visited the hospital as an outpatient for the first time in July 1949. *SR:* 44 mm/hr. *WBC:* 10,000/mm³. Eosinophils 8%. *X-ray of lungs:* Shadows of greatly enlarged lymph nodes in both hili but no lesions of the parenchyma or pleura visible. *Condition* (in 1949): General condition good. *Superficial lymph nodes:* No abnormality. *Heart and lungs:* No

abnormality. *Abdomen:* No abnormal masses felt. *Skin:* Several areas of infiltration on the face. *WR:* Negative. *Patho-anatomical* diagnosis (skin lesion): Schaumann's disease. *X-ray of bones:* There is fairly diffuse decalcification of the heads of the metacarpals and in the ends of the phalanges of the fingers. There are no lesions fully typical of Schaumann's disease but those which have been described might be the beginnings of such lesions. *X-ray of lungs* (Oct. 1949): Moderately diffuse and widespread fine speckling of both apical regions, more on one side than on the other. In Nov. the patient was admitted for an attack of biliary colic. Severe pains, nausea and vomiting. Sclerae yellow, urine dark. Radiography showed cholelithiasis and a poorly functioning gall bladder. She was considered to be inoperable and was therefore transferred from the surgical to the medical department. *Ophthalmological examination:* Chronic iritis. By Dec. the patient's condition had improved and her gall bladder was removed. A couple of nodes were found in the hepato-duodenal ligament and one about the size of a bean was excised. *Microscopic examination U. 10564/50* (Prof. Fåhræus): The lymph node shows marked changes. It is greatly fibrosed and shows only insignificant remains of the original parenchyma. There is a dense infiltration of rounded groups of epithelioid cells with numerous giant cells among the almost solid connective tissue. There is no caseous necrosis anywhere which makes it doubtful whether this is, in fact, a case of tuberculosis, though, in other ways it seems very like one. — In Jan. 1951 the patient again had erythema nodosum with chills and a rise of temperature up to 40° C. *X-ray of lungs:* Large hili. No definite parenchymal changes. *X-ray of lungs* (Jan. 1952): Increased density of both hili and increased linear markings around the hili but only insignificant glandular markings. *SR:* (Feb. 1952) 20 mm/hr.

Case 43. ♀, born 1898. Treated in hospital in 1942 under the diagnosis of bilateral pulmonary tuberculosis? Boeck's sarcoid?. No heredity for or known contact with tuberculosis. Never had erythema nodosum, pneumonia or pleurisy. Had increasing cough since about 1940. Visited a central dispensary in 1942. *X-ray of lungs:* Bilateral enlargement of the hili and a mottled streakiness in both lung fields (Fig. 28). Acid-fast rods were demonstrated in the sputum on two occasions during her stay in hospital and in June 1942 culture of tubercle bacilli was successful. "The suspicion that this might be a case of Boeck's sarcoid must therefore be abandoned." *Mantoux* (in Sept. 1942): Negative for 0.1 but positive for 1 mg. *Guinea pig test and culture on Loewenstein's medium:* Negative in both Sept. and Nov. 1942. — Repeated radiographs taken after discharge from the hospital showed that the lungs remained radiographically unchanged. Culture with gastric lavage fluid grew no tubercle bacilli. — In 1946 the patient began to feel breathless. Admitted to sanatorium in 1949 and treated there under the diagnosis of lymphogranulomatosis benigna (?). On discharge the following note was written: "The patient is suffering from a curious disease of the lungs. Many of the features are suggestive of Boeck's sarcoid but acid-fast rods have been successfully demonstrated at cultivation on Loewenstein's medium. She is tuberculin positive but not for amounts less than 1 mg. Has not improved under prolonged treatment." — The patient's condition grew worse shortly after discharge. She became breathless, tired and apathetic. She was readmitted to the sanatorium in Dec. 1950 and treated there under the diagnosis of lymphogranulomatosis benigna. Grew steadily worse during the spring with signs of circulatory failure and died in June 1951. *Autopsy U. 201/51* (author): There was a mass of rounded lymph nodes about the size of hazel nuts slightly adherent to one another and forming a conglomerate about the size of a hen's egg in the bifurcation of the trachea. Most of them were so hard and tough that it was very difficult to cut through them. Here and there fine crusts of calcification were found. There was a similar but smaller firm conglomerate of lymph nodes in each hilar region. There were also several nodes as hard as chalk and the size of date stones on the left side of

the trachea. Nowhere in the nodes was there any caseous necrosis. In the apices of the lungs there were areas which were very soft on palpation and on section were found to consist of a system, about the size of a hen's egg, made up of a number of small spaces, the walls of which were grey, smooth and even all over (Fig. 29). The lung tissue around the spaces was slate grey and indurated. No sign of caseation was seen anywhere. The rest of the lungs presented a very striking picture. There was a marking like a fine network, more clearly accentuated in the central part, radiating from each hilus and standing out against a darker bluish red background (Fig. 29). In these regions the lung tissue was very tough. There was no caseation. Closer examination of the arrangement of the affected intrapulmonary lymph nodes showed that, in many places both the pulmonary arteries and veins were compressed by the enlarged nodes impinging on them from outside. The heart showed the picture of chronic right sided failure. There were suspicions of small whitish specks here and there in the enlarged liver. The spleen was slightly enlarged. A dense white speckling could be glimpsed through the thin capsule and could also be seen on the shining, dark blue cut surface. *Microscopic examination:* There are large numbers of miliary-submiliary epithelioid cell tubercles with rather few giant cells of the Langhans type in them to be seen in the liver, lungs, spleen and lymph nodes. The giant cells in the lungs occasionally contain Schaumann bodies. Nowhere do the granulomata show caseous necrosis. There is, on the other hand, pronounced hyaline sclerosis. The spaces noticed in the apices of the lungs are seen to be lined with a simple or compound epithelium, sometimes taking the form of a squamous epithelium (healed cavities? bronchiectases?). *Patho-anatomical diagnosis:* Chronic lymphogranulomatosis benigna; pulmonary fibrosis; right heart failure.

Case 44. ♂, born 1899. Treated in hospital in 1951 under the diagnosis of lymphogranuloma benignum. Had a gastric ulcer at the age of 33. No heredity for tuberculosis. Much troubled by breathlessness during the past years. The lungs were examined in Dec. 1949 in connection with a broken bone. There were widespread net-like opacities disseminated interstitially in both lung fields. — They were most dense and massive in the bases, particularly below and lateral to the hilar shadows. There was slight thickening of the interlobar pleura on both sides. Etiology uncertain. *Mantoux:* 1 mg negative. *SR:* 5 mm/hr. Biopsy of a lymph node. *Microscopic examination V. 1334/51* (I. Behring, M.D.): The lymph nodes is tightly packed with foci of epithelioid cells and giant cells without any trace of a tendency to necrosis, and without any marked perifocal lymphocytic reaction. The microscopic picture is more like that of Schaumann's disease than that of tuberculosis.

Case 45. ♂, born 1914. Treated in hospital in 1951 under the diagnosis of lymphogranulomatosis benigna. No heredity for tuberculosis. Increasing enlargement of the lymph nodes on the sides of the neck and in the groins since the summer of 1950. No feeling of illness. Went to hospital because the swelling of the lymph nodes was considered unsightly. *On admission:* General condition good. *Superficial lymph nodes:* There are a number of nodes in the axillae between the sizes of a pea and a pigeon's egg, in the groins they are between the sizes of a pea and a hazel nut. Along the margin of the lower jaw and the posterior border of the sternocleidomastoid there are large numbers of nodes between the sizes of grains of wheat and pigeon's eggs. They are all painless and freely mobile. *Abdomen:* No abnormal masses palpable. Remained afebrile throughout the stay in hospital. *SR:* 25 mm/hr. *WR:* negative. *Mantoux:* 10 mg negative. No radiographically demonstrable enlargement of the spleen. *X-ray of bones of hands:* No abnormality. *X-ray of lungs* (April 1951): Scattered thin specks of opacity in the upper third of the left lung. Tuberculosis? *Ophthalmological examination:* No abnormality. *WBC:* 3,100/mm³. Eosinophils 8%, monocytes 13%. *Fractional serum protein*

determination: Total protein 7.8 %, albumin 2.9 %, globulin 4.9 %. A/G 0.6. *Culture on Loewenstein's medium:* Negative ,using gastric lavage fluid. Biopsy of a lymph node from the neck. *Microscopic examination U. 2929/51* (S. Ranström, M.D.): The lymph node is crammed with epithelioid cell tubercles. Definite tendency to induration. Insignificant amount of caseation. *Patho-anatomical diagnosis:* Lymphogranulomatosis benigna. — The patient was treated with streptomycin and PAS. *Repeat X-ray of lungs* (May 1951): No significant change. *X-ray of lungs* (Aug. 1951): The opacities in the upper parts of the left lung have probably diminished. There are very slight opacities left on the level of the clavicle and in the space between the clavicle and the first rib laterally. There is also an indefinite shadow in the lateral parts of the first and second intercostal spaces on the right side. The hilar shadows are large and dense.

Case 46. ♀, born 1895. Treated in hospital in 1951 under the diagnosis of Schaumann's disease. No heredity for or known contact with tuberculosis. Cholecystectomy in 1950. Felt tired and breathless after the operation. Became acutely ill in Aug. 1951 with pain in the right side of the chest, chills and a temperature of about 40° C. The temperature fell after a couple of days' treatment with penicillin and then remained just above normal. *X-ray of lungs* (Sept. 1951): In the upper mediastinum there are lobulated bulges in both sides of the mediastinal shadow projecting a couple of finger's breadths from the mid line and together forming a conglomerate almost as large as an orange. No lesions of the parenchyma of the lungs. *Diagnosis:* Lymphogranulomatosis Sternberg ? — Admitted to hospital for further investigation. *On admission:* General condition good. *SR:* 43 mm/hr. *Superficial lymph nodes:* No enlarged nodes palpable. *RBC:* 4.5 mil/mm³. *WBC:* 7,000/mm³. *Mantoux:* 1 mg negative. Biopsy of a lymph node. *Microscopic examination V. 4142/51* (I. Behring, M.D.): The lymph node is tightly packed with foci of epithelioid cells and giant cells without any trace of caseous necrosis. Schaumann's disease is the most probable diagnosis. — Repeated radiographic examinations of the lungs during 1951 showed no change compared with the picture taken in Sept. 1951. Treated with radiotherapy to the hili, fortedol + streptomycin. In Feb. 1952 the lungs were radiographically normal.

Case 47. ♀, born 1912. Treated in hospital in 1951 under the diagnosis of acute bilateral iritis (Schaumann's disease). The patient's sister had had arthritis of the hip followed by tubercles of one eye. Otherwise no family history of tuberculosis. — Redness of the eyes for some days in Sept. 1951. A week or two later the redness returned with pain. Impaired vision. *Ophthalmological investigation:* Iritis acuta bilat. *SR:* 35 mm/hr. *WBC:* 5,100/mm³. Eosinophils 7 %, monocytes 7 %. *Mantoux:* 0.01 mg positive. *X-ray of lungs:* Sharply defined, lobulated, glandular shadows in both hilar regions forming masses the size of eggs. No lesion of the parenchyma. *X-ray of sinuses:* Right maxillary sinus solidly opaque. *WR:* Negative. *AST:* 125 units/ml. *Fractional serum protein determination:* Total protein 7 %, albumin 4 %, globulin 3 %. A/G 1.4. Biopsy of a lymph node. *Microscopic examination V. 4583/51* (I. Behring, M.D.): The lymph node is tightly packed with foci of epithelioid cells and giant cells without any sign of caseous necrosis or marked perifocal reaction. Probably Schaumann's disease. — In Jan. 1952 the eyes had almost returned to normal. *X-ray of lungs:* Regression of the hilar changes but slight increase in the markings in the parenchyma. *SR:* 37 mm/hr. In May 1952 the lungs were radiographically normal.

Case 48. ♀, born 1909. Treated in hospital in 1952 under the diagnosis of lymphogranulomatosis benigna. No heredity for or known contact with tuberculosis. The patient began to feel tired and to have aches in the knees and ankles in Aug. 1952. A week or two later some bluish red, tender, raised lumps about 3 cm in diameter appeared on both shins. *SR:* Never above 45 mm/hr. Hacking

cough since Nov. 1952 and slight fever almost all the time since Aug. 1952. Dryness of the mouth and a feeling as of sand in the eyes. *On admission:* General condition satisfactory. *Superficial lymph nodes:* There is an elastic, slightly tender, freely moveable lymph node barely the size of a bean in the right supraclavicular fossa. *SR:* About 70 mm/hr. *Mantoux:* 0.01 mg positive. *X-ray of lungs:* Large dense hilar shadows partly caused by enlargement of the nodes and partly by perihilar infiltration. The picture is very like that seen in Schaumann's disease. *X-ray of bones of hands:* No abnormality. Biopsy of a lymph node from the right supraclavicular fossa. *Microscopic examination U. 1483/52* (Prof. Gellerstedt): The node is densely infiltrated with submiliary tubercles with a tendency to fibrosis between them. The picture corresponds exactly with that seen in Schaumann's disease. *Patho-anatomical diagnosis:* Atypical tuberculosis.

Case 49. ♀, born 1912. Treated in hospital in 1943 under the diagnosis of subchronic uveoparotid fever and in 1952 under the diagnosis of lymphogranulomatosis benigna (Schaumann's disease) + myocardial degeneration. Became ill in Aug. 1952 with headache. In Sept. 1942 swelling of both eyelids. It disappeared after a couple of days. In Nov. 1942 left-sided facial paresis which disappeared after a couple of weeks. Eyesight deteriorated gradually so that by Christmas time the patient could not read. The physician found uveitis. Some dizziness from time to time since 1943. *On admission* (in 1943): General condition good. No sign of cardiac decompensation. *Superficial lymph nodes:* No abnormality. *X-ray of skeleton:* No abnormality. *X-ray of lungs:* Enlargement of right hilar nodes. *SR* and *WBC:* Normal values. Cough since 1949 and increasing breathlessness since 1951. In 1950 the patient noticed enlarged lymph nodes in both axillae. A number of nodes gradually made an appearance in both sides of the neck, particularly under the left angle of the jaw recently. *On admission* (1952): General condition satisfactory. *Superficial lymph nodes:* There are a number of freely movable lymph nodes about the size of peas or beans on both sides of the neck, in the submandibular region, particularly round the left angle of the jaw and down the posterior border of the sternocleidomastoid. There are also some elastic, painless nodes ranging in size from that of a walnut to that of a hen's egg in the axillae, and a couple the size of beans in the groins. *SR* and *WBC:* Normal values. *Mantoux:* 1 mg negative. *X-ray of lungs:* Widespread changes especially in the basal part of the right lung looking like those seen in Schaumann's disease. *X-ray of bones of hands:* A couple of punched out areas of decalcification in the bones of some of the fingers. — Extirpation of a lymph node from the neck. *Microscopic examination U. 4649/52* (Prof. Gellerstedt): The node is diffusely and closely packed with submiliary tubercles without caseous necrosis and with only occasional giant cells and with a certain tendency to sclerosis of the basal reticulum. The picture is completely in accord with that seen in Schaumann's disease. *Patho-anatomical diagnosis:* Atypical tuberculosis.

Case 50. ♀, born 1914. Treated in hospital in 1952 under the diagnosis of lymphogranulomatosis benigna. No heredity for tuberculosis. Had a baby in July 1952. In Oct. 1952 became ill with cough and sore throat. Stiffness of the joints after a week. A couple of weeks later still became feverish and apathetic. In the beginning of Nov. 1952 erythema nodosum. Tuberculin test negative. *X-ray of lungs* (Nov. 1952): No abnormality. Fever gradually disappeared. New eruptions of erythema nodosum associated with a rise in temperature appeared in Dec. 1952. Admitted to hospital for cortisone treatment. *Superficial lymph nodes:* There is a fairly soft, painless lymph node the size of an almond in the left supraclavicular fossa. *WBC:* 5,700/mm³. Eosinophils 12 %, monocytes 7 %. *SR:* Variable between 29 and 97 mm/hr. Removal of a lymph node. *Microscopic examination U. 12044/52* (Prof. Fåhræus): An enlarged lymph node very densely infiltrated with tubercles. Occasional giant cells. No caseous necrosis. Typical picture. *Patho-anatomical*

diagnosis: Atypical tuberculosis (Schaumann's disease). The patient's temperature remained about 38° C during the spring of 1953. After the institution of cortisone treatment it fell immediately and the patient felt perfectly well. *X-ray of lungs* (Dec. 1952): Since the last radiograph was taken there has been an enlargement and increase in density of both hilar regions with increased markings, especially in the basal regions. No definite shadows of enlarged lymph nodes in the hili. There is an opacity which looks like a node in the paratracheal region on the right side. It is barely the size of the tip of a thumb and is well defined laterally. *X-ray of bones of hand:* Nothing noteworthy.

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